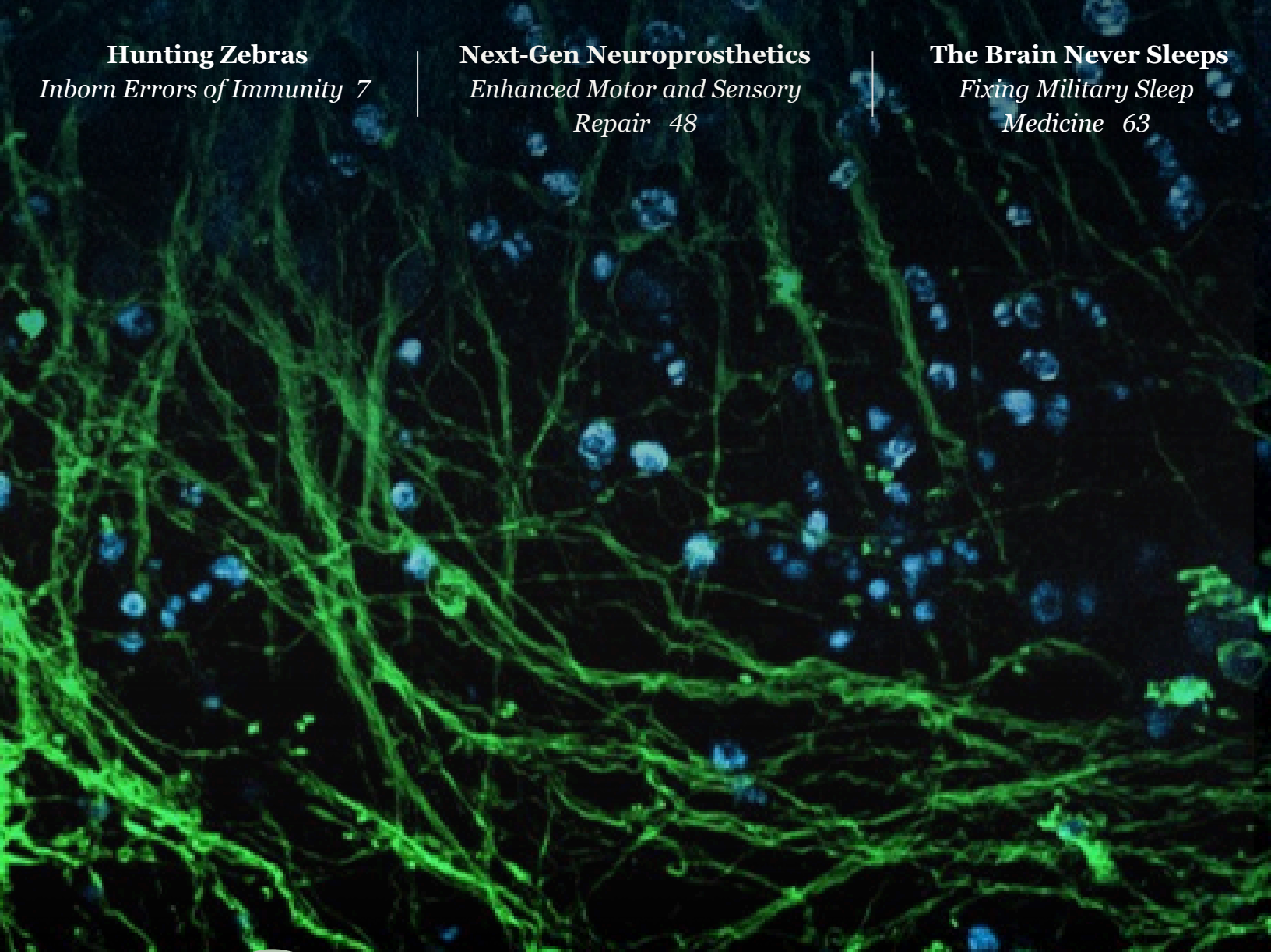

USU Science Review

A human cortical organoid derived from induced pluripotent stem cells. Image courtesy of Bradley Smith and the Juliano & Burnett Laboratories. ***p. 43***

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From the Editors

USU Science Review, a student-led 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. From its inaugural issue in November 2022, the journal has witnessed tremendous growth. We have expanded the editorial staff to include both graduate and medical students and broadened authorship to keep the collaborative spirit of scientific communication. The dissemination of research findings and clinical perspectives, discussion of topics between students and faculty, and firsthand accounts of scientific conferences represent invaluable contributions to the scientific community and beyond.

We thank the authors for their time and contributions to this issue, as well as the many faculty members and students who offered helpful feedback and spirited conversations. Future issues will be managed and edited by an editorial team of graduate students who have advanced to candidacy - we invite interested students to reach out to ususcireview@googlegroups.com. We additionally extend a warm welcome to faculty and student writers interested in submitting to this periodical.

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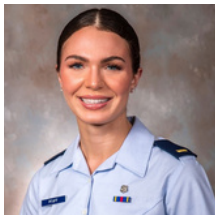
Junior editors	 2LT Rabea Pfaff	 Yoland Victor	 Piper Deleon	 Miranda Janvrin	 Russell Maloney	 2LT Lily Haghpassand

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The faculty perspectives section is designed to encompass both opinion pieces and histories of the field from leading scientific experts at USU.

Hunting Zebras: Lessons from the Study of Human Inborn Errors of Immunity

By Andrew Snow, PhD

Reductionism & Human Immunology

I consider myself a simple-minded immunologist. Self-deprecation aside, this assessment reflects my "traditional" scientific training as a reductionist. Complex biological phenomena are often best understood by breaking them into simpler components. To understand the function(s) of a gene, a reductionist approach entails altering the expression or function of the encoded protein in an appropriate biological context, from single cells to whole organisms. One gene at a time – delete it, overexpress it, mutate it, or inhibit its enzymatic activity. Observe the consequences. This is an approach my simple brain can grasp. Hopefully there is a testable hypothesis included somewhere in there.

For decades, immunological research has adhered to a reductionist mindset by relying heavily upon transgenic/knockout mouse models. Although we have learned a lot, the use of inbred mice ignores the vast genetic diversity of the human population, not to mention varied environmental and microbial exposures.[1] Indeed, findings derived from many animal models often do not faithfully replicate the etiology and diversity of human diseases,[2] perhaps explaining why so many promising drug candidates ultimately fail in clinical trials.[3] This sobering realization has spurred greater emphasis on the study of human immunology in recent years.

In the current era of systems biology and reliable next generation sequencing (NGS), the reductionist approach may appear myopic, especially when studying humans. Emergent properties that only arise from systems-level interactions can easily be overlooked. Unbiased "multiomic" profiling can reveal patterns we might never imagine by focusing on a specific genotype, unmasking novel insights even in the absence of a specific hypothesis. We must continue to embrace these rapidly evolving technological capabilities, especially now that we can extract so much information from a relatively small blood or tissue sample.[4]

Nevertheless, I remain confident that we can still learn so much from the reductionist mindset in studying our own biology. Expanding research on patients with monogenic "inborn errors of immunity" (IEI) underscores this point, providing invaluable, often surprising lessons about human immunology by examining the consequences of a single gene alteration.[5] Clinicians have traditionally been trained to favor more commonplace explanations over rarer exotic diagnoses. As Dr. Theodore Woodward's famous aphorism suggested, many medical students are still told that "when you hear hoofbeats behind you, don't expect to see a zebra." Think horses, not zebras.[6] As human-focused immunological research accelerates, the IEI field largely rejects this argument, recognizing that profound biological insights are often drawn from the exception rather than the rule. Once dismissed as rare "medical curiosities", IEIs have repeatedly proven to be the most instructive and unbiased "experiments of nature" for understanding human immunity.[7] In short, we cannot ignore zebras in medicine.

Complex biological phenomena are often best understood by breaking them into simpler components.

By aggregating the more than 550 distinct monogenic IEIs [inborn errors of immunity], we find a collective incidence of approximately 1 in 1,200 individuals, constituting a disease burden comparable to … immune disorders such as multiple sclerosis.

Once considered a niche field, the elucidation of monogenic causes for IEIs has exploded exponentially over the past ~15 years as NGS has become widely accessible.[5] Beyond telltale recurrent infections early in life, IEIs can encompass a diverse range of clinical manifestations including autoimmunity, inflammation, malignancy, allergy, and other signs of immune dysregulation. By aggregating the >550 distinct monogenic IEIs defined to date based on this broader classification, we find a collective incidence of approximately 1:1,200 individuals,[8,9] constituting a disease burden comparable to well-known polygenic immune disorders such as multiple sclerosis (MS). Strikingly, IEI-related genes account for ~10% of all single gene lesions that are known to underlie human phenotypes (n=5,045, www.omim.gov). Furthermore, this math suggests there are ~8,000 IEI patients within the Military Health System (MHS), most of whom remain genetically undiagnosed. Thus for both civilian and military physicians, recognizing these disorders is essential to delivering precise, genotype-informed care to a traditionally underserved population.

Lessons from history: early IEI research

The history of this field is punctuated by many seminal clinical discoveries that illuminated central tenets of immunology, which arguably began in military medicine.[10] While serving at Walter Reed Army Hospital in 1952, Colonel Ogden Bruton encountered a young boy who suffered from repeated, life-threatening bacterial infections and bouts of sepsis. Hypothesizing that his patient might be incapable of generating antibodies against any organism, Bruton employed a new “electrophoresis” technique to analyze his serum proteins, revealing a total absence of the "gamma globulin" fraction (i.e., IgG). Remarkably, monthly administration of subcutaneous human serum globulin restored serum IgG levels and eliminated all infections and septic episodes. The emergence of similar cases in young males shortly thereafter bolstered the classification of this disorder as X-linked agammaglobulinemia (XLA).[11]

Although a few other primary immunodeficiencies had been recognized by then,[12] Bruton’s landmark study was the first to describe the laboratory diagnosis and successful treatment of an IEI. He also postulated that the boy’s disease represented a “congenital dysfunction”, even though the causative gene encoding for Bruton’s tyrosine kinase (BTK) was not discovered until 1993.[13,14] In essence, Bruton’s pioneering work established that a specific monogenic defect could result in complete failure of a specific arm of the adaptive immune system, which paved the way for delineating the role of B cells and antibodies in host defense. More importantly, immunoglobulin replacement remains a bedrock “passive immunity” therapy for many B cell-related disorders regardless of genetic etiology,[15] including humoral immune deficits that remain genetically undefined (e.g., common variable immunodeficiency).[16]

Momentum generated by Bruton's discovery continued through the 20th century, culminating in the description of IEIs related to distinct immune deficits in phagocyte function (e.g. chronic granulomatous disease),[17] complement (systemic lupus erythematosus),[18,19] and T lymphocyte function.[20] The latter was most famously illustrated by the case of David Vetter, the "boy in the bubble". His battle with X-linked severe combined immunodeficiency (SCID) was well documented throughout the 1970s, forcing David to live in isolated sterile environments before he succumbed to infectious complications after bone marrow transplant at age 12. In 1993, X-linked SCID was linked to deleterious mutations in the *IL2RG* gene, illuminating the critical role of the "common gamma chain" in T cell development and cytokine signaling.[21] We now appreciate that deleterious mutations in multiple genes required for CD4+ T cell development or function can result in SCID, reflecting life-threatening defects in both cellular and humoral immunity.[22] Fortunately, this research prompted the widescale adoption of newborn screening for SCID, directing patients to rapid curative hematopoietic stem cell transplantation before dying from devastating opportunistic infections.[23] Moreover, this work spurred the development of the first successful gene therapies for various forms of SCID,[24] where a defective gene could effectively be replaced with a normal copy in the patient's hematopoietic stem cells and autologously transplanted to restore immune function.

The expanding constellation of IEIs

In recent years, next-generation sequencing has rapidly accelerated the discovery of new IEIs. Based on the 2024 update from the International Union of Immunological Societies, we now recognize 559 distinct IEIs organized into 10 phenotypic classification groups, including 67 novel monogenic defects discovered since 2022.[8,9] As mentioned above, IEIs collectively represent an enormous spectrum of immune dysregulation affecting both innate and adaptive immune defenses, spanning from exquisite sensitivities to single pathogens (e.g. herpes simplex encephalitis caused by loss-of-function mutations in TLR3 or UNC93B)[25,26] to complex syndromes (e.g. autosomal recessive or dominant hyper-IgE syndromes).[27] IEI research also helped to establish a genetic basis for autoimmunity and autoinflammation in patients with AIRE deficiency and type I interferonopathies, respectively, just to name a few examples.[28-30] In fact, the 2025 Nobel Prize in Medicine was awarded to three researchers for their groundbreaking work on regulatory T cells (Tregs), including the discovery of mutations in FOXP3 (the master transcription factor required for Treg development) as the cause of severe autoimmunity in both humans and mice.[31-34] Having worked in the IEI field for ~20 years, I am constantly astonished by the pace and brilliance of these immunological discoveries, which show no sign of slowing down soon. This rewarding work fosters unprecedented global collaboration among a tight-knit community of clinical and basic researchers that have learned to recognize the "zebras" and devise precision treatments for them. My laboratory has helped to discover and characterize IEIs caused by pathogenic variants in the lymphocyte scaffold molecule CARD11,[35] and ongoing collaborative work with Dr. Clifton Dalgard, Dr. Nathan Boggs, and other USU colleagues aims to improve the diagnosis and treatment of IEI patients within the MHS. I am honored and humbled to be part of this dynamic field – and wow, it is fun!

Even at this breakneck pace of discovery, many mysteries remain in the study of human immune disorders, indicating that simple Mendelian genetics cannot explain everything. For many IEIs, we are still grappling with the sticky questions

of incomplete penetrance (why some mutation carriers get sick while others do not) and variable expressivity (why the same mutation causes different symptoms in different people), even within the same family.[7,36] Genotype-phenotype correlations remain nebulous for many IEI genes, even as large-scale genomic biobanks and enhanced *in silico* prediction algorithms enable powerful new bioinformatics approaches to this problem. Far from discouraging, these thorny problems bolster more excitement and innovation in the field; incredible recent insights have begun to provide some clarity. For example, there is growing recognition of non-Mendelian "clinical copycats" of IEIs, driven by somatic gene variants or the development of autoantibodies against key host defense proteins.[37,38] Indeed, the presence of neutralizing autoantibodies against type I interferons accounts for nearly 10% of critical COVID-19 cases – a discovery enabled by a consortium of IEI investigators.[39,40] Newer work highlights the influence of common genetic modifiers and monoallelic expression in elucidating mechanisms of incomplete penetrance,[41,42] emphasizing important roles for epigenetic and environmental factors in shaping immune phenotypes in humans.[43] As these discoveries continue to reveal novel insights on human immunity, a common theme emerges: the "rare" informs the "common". Consequently, as biomedical researchers and educators, we must train the next generation of clinicians to recognize the "red flags" of IEIs, and appreciate the perspective that IEI research can offer regarding how healthy human immune homeostasis is maintained.[7]

Maybe "rare" is more common than we thought

As we diagnose more patients with rare monogenic IEIs, I think single gene variants may be more important in explaining common diseases than we once thought. Despite conventional wisdom, many "common" single-gene variants are now recognized to influence disease.

When you hear hoofbeats behind you, don't expect to see a zebra… The IEI field largely rejects this argument… Profound biological insights are often drawn from the exception rather than the rule.

For example, a common tyrosine kinase enzyme (*TYK2)* missense variant in Europeans explains recessive susceptibility to tuberculosis,[44] whereas null interferon alpha receptor variants commonly found in Pacific and Arctic populations predispose to severe viral infections.[45,46] Large genomic biobank analyses have uncovered more pathogenic variants in substantial cohorts of clinical trial patients with inflammatory bowel disease (IBD), MS and atopic dermatitis.[44] Immune dysregulation is also garnering more attention in well-established chromosomal abnormalities such as trisomy 21 (Down syndrome),[47] informed by earlier IEI research on established chromosomal aberrations such as 22q11.2 deletion (DiGeorge syndrome).[48] Finally, autoantibodies against critical cytokines such as IL-10 and GM-CSF may explain idiopathic cases of IBD and pulmonary alveolar proteinosis, representing phenocopies of much rarer monogenic IEIs.[49-51] Thus even as we appreciate

the mind-boggling complexity of human genetics, it may be worth entertaining a monogenic cause for many patient phenotypes, provided those phenotypes are carefully described. Arguably this approach can offer more meaningful insights on disease pathogenesis compared to genome-wide association studies, which identify statistical correlations across populations without necessarily pinpointing a specific disease-causing genotype.[52]

As we continue to develop rigorous mechanistic approaches for ascertaining the functional impact of "variants of unknown significance", NGS empowers us to define specific monogenic causes of immunological disease in more and more patients. This transition from statistical probability to molecular certainty promises to transform how we diagnose and treat rare and common diseases. Perhaps simple-minded reductionist thinking still holds value; think one gene at a time, observe the consequences. Maybe there are more zebras in the herd than we thought.

About the Author

Dr. Snow is a Professor in the Department of Pharmacology and Molecular Therapeutics, and Director of the Emerging Infectious Diseases Ph.D. Program at USU. His laboratory studies mechanisms of human leukocyte signaling and cell death, particularly as they relate to inborn errors of immunity.

AI Statement: The author acknowledges the use of Gemini 3.5. AI was used for initial brainstorming/idea generation. All AI-generated suggestions were reviewed, revised, and approved by the author, who takes full responsibility for the accuracy and integrity of the work.

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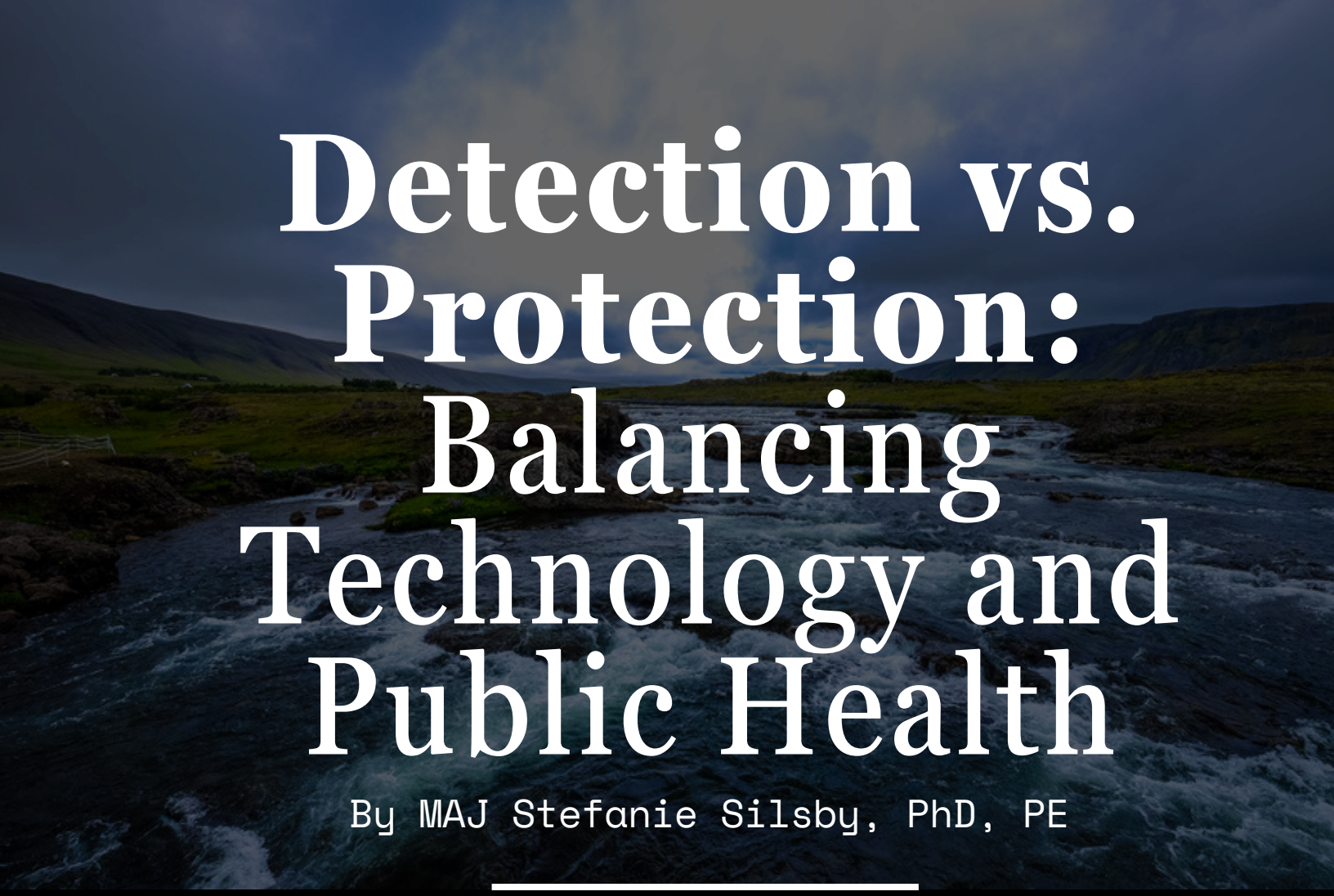
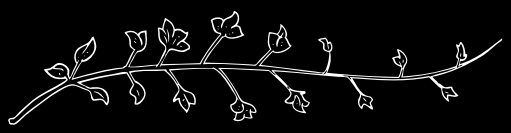


Detection vs. Protection: Balancing Technology and Public Health

By MAJ Stefanie Silsby, PhD, PE

We are exceptionally good at developing novel scientific technologies, but are often blindsided by the unexpected ethical and policy issues they create. Today, environmental health faces this exact hurdle: Instead of simply detecting threats, how low must we quantify them and where does public safety end and economic burden begin? Modern analytical instrumentations, such as gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-mass spectrometry (LC-MS) instruments, can now confidently measure potentially harmful compounds in our air, water, and soil at previously undetectable trace concentrations, reaching parts per trillion and even parts per quadrillion, which are equivalent to a single drop of water in 20 or 20,000 Olympic-sized pools, respectively.[1,2] These technological advances can expose the widespread presence of man-made compounds and contaminants of emerging concerns. However, their capabilities have challenged traditional environmental health risk assessment methods, thereby impacting public health and policy decisions. For example, the link between the presence of trace substances, down to parts per quadrillion levels, may only be useful if their risk is supported by toxicity assessments. To ensure both public safety and economic viability, we must balance technological progress, which continuously increases the specificity measurement of a substance, such as the limit of quantification (LOQ), and assess exposure thresholds below which risks to human health are negligible.[3] The critical question of environmental

health today is no longer "Can we detect it?" but "How far down must we quantify to ensure protection without imposing unnecessary economic burdens?"



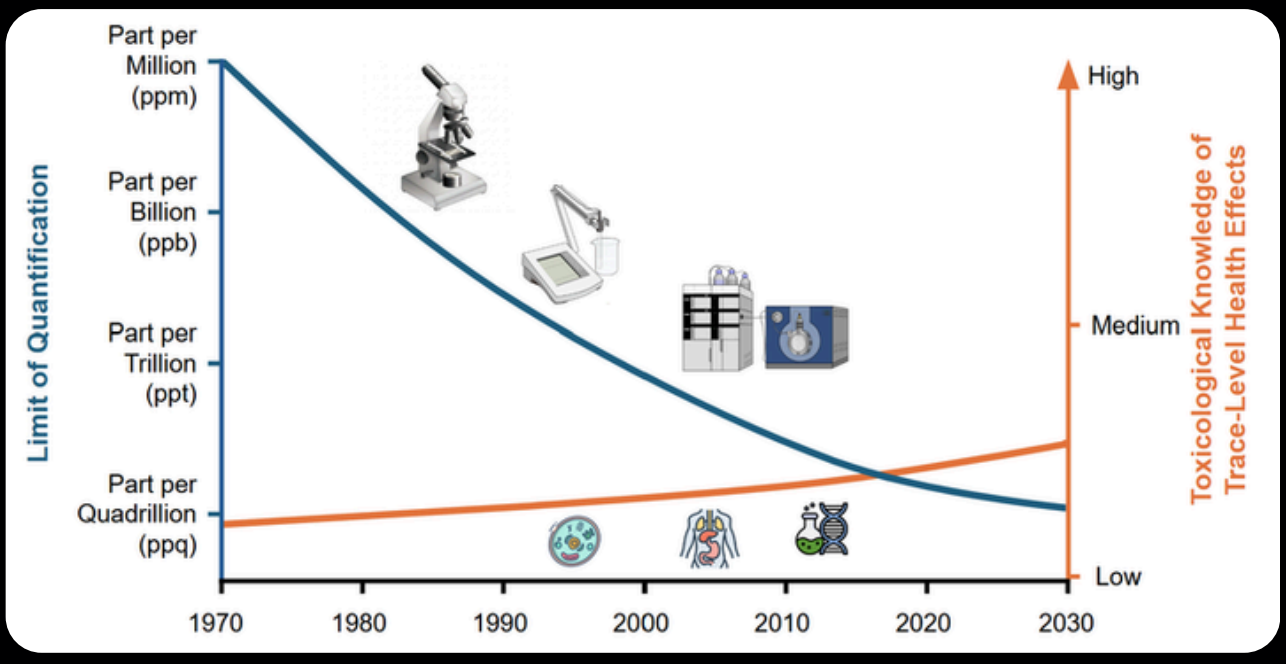
For decades, United States environmental policy has relied on this precautionary principle,[4] especially regarding chemicals known or suspected to be carcinogenic, such as lead, benzene, or the per- and polyfluoroalkyl substances (PFAS). This principle suggests that we should accept the concept that “when an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically.”[4] In practice, under this principle, if the best available data suggests a significant threat, despite a level of uncertainty among scientists, policymakers are obligated to act to provide the highest protection to human health. For substances that are known or suspected to cause cancer, this philosophy is often formalized through the linear no-threshold dose-response relationship in human health risk assessments, which suggests that there is no “safe” level of exposure for certain compounds, i.e., concentrations above zero; even very small doses are assumed to carry a measurable, quantifiable risk.[5] Applying this philosophy requires regulators to chase an analytical zero, setting standards based on what can be detected rather than what is necessary. As a result, regulatory standards such as Maximum Contaminant Levels (MCLs)[6] and National Ambient Air Quality Standards (NAAQS)[7] specific to drinking water and ambient air, respectively, are increasingly dictated by modern instrumentation. Even though this approach aims for maximum safety and human protection, its strict application creates significant regulatory challenges. For example, when a new U.S. Environmental Protection Agency (EPA) rule mandates an MCL for a PFAS compound at 4 parts per trillion,[6] it raises essential questions: Is the regulatory target based on comprehensive human health toxicity assessments,[8] or is it merely the lowest level analytical instrumentation can currently confidently measure? If new tools can detect 0.1 parts per trillion tomorrow, will the standard shift again?

How far down must we quantify to ensure protection without imposing unnecessary economic burdens?

Scientific experts remain divided on whether trace amounts of carcinogens truly threaten public health or if our biological systems are equipped to handle them. On one side of the debate, the linear no-threshold model assumes that any level of exposure, no matter how small, carries a potential risk of cancer. Conversely, many researchers argue for a threshold-based approach, suggesting that there is a "safe zone" for exposure.[9] They suggest that at low concentrations, the body’s natural metabolic and repair systems can effectively neutralize certain harmful substances. Some scientists even suggest that these minor exposures may trigger hormesis, a process where low-level stress actually stimulates beneficial biological defenses.[10] Failing to account for these natural defense mechanisms may lead to significant misallocation of public resources towards an analytical zero, focused on policy and efforts to reach a negligible difference in substance pollution. By shifting our perspective, we could instead invest those resources into high-efficacy areas that offer guaranteed public health benefits, such as

improving access to nutritious foods and promoting physical fitness across the population.[11] Transitioning regulatory standards from parts per billion to parts per trillion is a significant undertaking, as it requires a thousand-fold increase in analytical sensitivity and economical burden. Testing at such low limits requires highly specialized and expensive laboratory equipment that many local facilities do not possess, resulting in immense investment to modernize existing analytical detection capabilities and laboratory equipment or outsource analysis to commercial laboratories. Using drinking water utilities as an example, the financial burden of these upgrades necessary to provide drinking water that meets regulatory requirements often falls directly on local ratepayers.[12] This can lead to an increase in utility costs, potentially making basic water bills unaffordable for low-income families who are already struggling with a rising cost of living. Beyond the analytical cost, monitoring at the parts per trillion level leaves no room for error; even trace amounts of outside contamination can skew results,[13] triggering false alarms and leading to unnecessary, costly remediation. Toxicologists and regulators often study exposures to a single substance and its associated health effects while ignoring the cocktail effect.[14] In reality, our body is exposed to hundreds of pollutants simultaneously, and we still do not fully understand how these substances interact with one another. Despite clear evidence of the cocktail effect, toxicological studies that evaluate the combined effect of multiple chemicals are challenging due to the sheer number of potential combinations.[15] To reduce the amount of potentially hazardous substances in our environment and to better protect public health, we must therefore shift our strategy toward prevention, i.e., stopping pollution at its source rather than trying to manage it after it has already entered the environment. While safer alternatives or engineering controls in the form of pollution control and treatment devices are helpful for mitigating the number of substances that can contribute to the cocktail effect, their success largely depends on the precision and sensitivity of analytical instruments to confirm the absence of these harmful substances in our environment.

Figure 1: The growing gap between detection and interpretation. While modern technology allows us to detect chemicals at the part-per-quadrillion level, our biological understanding of how these trace contaminants affect human health remains a challenge for risk assessments.



Though advanced analytical instruments quantify potentially harmful substances in our environment, our ability to detect substances at trace-level concentration should not automatically trigger more stringent regulations. Instead, the future of environmental health requires a more nuanced approach. We must recognize that while our analytical instruments may grow increasingly more sensitive with no limit, our policies must be guided by clear biological evidence of actual risk for the parts per quadrillion level when it exists, not necessarily by the precautionary principle. While we must continue to advance our analytical capabilities, as these tools are essential for identifying existing and emerging threats, we must also decouple the capability to detect a substance from the requirement to regulate. Only then can we ensure that we are not just measuring the world more precisely, but actually making it safer.

About the Author

Dr. Silsby is a Professor in the Department of Preventive Medicine and Biostatistics, Occupational and Environmental Health Sciences Division at USU.

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When Proteins Became Not-So-Permanent

By Jordan VerPlank, PhD

The discovery of protein turnover

The concept of protein turnover is only approximately 80 years old. Before then, proteins were viewed as stable constituents of cells and tissues. Some scientists allowed for the possibility that proteins might be subject to 'minor wear and tear,' but in the complete absence of evidence for or against, everyone accepted that proteins were permanent. Dietary proteins were thought to provide the organism with energy and nothing else. The tools to demonstrate otherwise were unavailable. To detect degradation of a protein, one would have to tag it in a way that it could then be tracked. Radioisotopes had been developed in the early 1910s, but they were not suitable for labeling amino acids.

The first of what would be several challengers of the scientific status quo in this story was Rudolf Schoenheimer. In the 1930s, he fled Nazi Germany and established a laboratory at Columbia University. One of Schoenheimer's early trainees was David Rittenberg, who joined the lab after completing his PhD under Harold Urey. Urey was famous at the time for winning the Nobel Prize in Chemistry in 1934 for his discovery of deuterium. Not satisfied with developing only one stable isotopic tracer, Urey also enriched heavy nitrogen (^{15}N), which Schoenheimer and Rittenberg realized could label amino acids in a way that was biologically indistinguishable from the natural analogs for studies of protein dynamics. They administered ^{15}N-labeled tyrosine to rats. If proteins were static, as everyone believed, ^{15}N-labeled amino acids would appear almost entirely in the urine. They did not. Only 50% of the labeled amino acid was in the urine. The other 50% was found in proteins throughout the rats' tissues, not only as labeled tyrosine but also as an αNH_2 group in other amino acids. These experiments showed that proteins in the body are in a dynamic state of

synthesis and breakdown. Schoenheimer presented these revolutionary findings twice. After he tragically took his own life in 1941, his colleagues turned his lecture notes into the book, "The Dynamic State of Body Constituents."[1] The idea of protein turnover spread, but was considered radical and still challenged well into the 1950s. If proteins were being turned over, what was degrading them?

The discovery of the lysosome

Christian de Duve was not studying protein degradation in 1949. He was interested in understanding how insulin altered glucose metabolism in the liver and was performing differential centrifugation to find out where the enzyme glucose-6-phosphatase was located in hepatocytes. As controls in these experiments, he also looked for the location of acid phosphatase and other hydrolytic enzymes in the gradient after centrifugation. De Duve noticed that several hydrolytic enzymes were found together in the same fraction of the gradient, suggesting that they resided in the same cellular compartment. He also noticed that when the hepatocyte fractions were damaged by freeze-thaw or harsh methods of homogenization, the activity of acid phosphatase increased. Both were methods that broke down lipid membranes. From these observations, he hypothesized the existence of a "new membrane-bound organelle specialized for intracellular digestion."[2] De Duve named it the lysosome. He then characterized lysosomes biochemically and confirmed their existence by electron microscopy. For this work, he was a co-recipient of the Nobel Prize in Physiology or Medicine in 1974.

The (temporary) supremacy of the lysosome

The discovery of the lysosome in 1955 seemed to answer once and for all the question of how proteins were degraded in cells. It just made sense. Here was a membrane-bound sac filled with hydrolytic enzymes, separated from the rest of the cell. Proteins could be delivered to the lysosome for destruction, and all other components of the cell could be protected from accidental degradation. If intracellular protein breakdown occurred only in the lysosome, the only remaining question, as far as most were concerned, was how proteins got there. The answer to that question would be autophagy, whose mechanisms would not be worked out until decades later.[3] But even as the lysosome became widely accepted as the major, if not sole, site of intracellular protein breakdown, observations were reported throughout the 1960s and 1970s that could not be reconciled with the idea. Different proteins had different half-lives.[4,5] Some disappeared quickly, while others were much more stable. The rates of degradation of some proteins also changed under physiological and pathophysiological conditions,[6] and inhibitors of lysosomal enzymes did not block the degradation of all proteins.[7] The lysosome could not be the whole story.

Embrace anomalies, trust your data, and remember that opportunities may be hidden in the problems that everyone else considers solved.

A second system

The strongest challenge to the idea that the lysosome was the sole source of intracellular degradation was the study published in 1977 by Joseph Etlinger and Alfred Goldberg.[8] They

showed in rabbit reticulocytes, which lack lysosomes, that abnormal hemoglobin was degraded via a process that required ATP. It was not obvious to anyone at the time why protein degradation would require energy. In fact, the breaking of a peptide bond should release some energy.

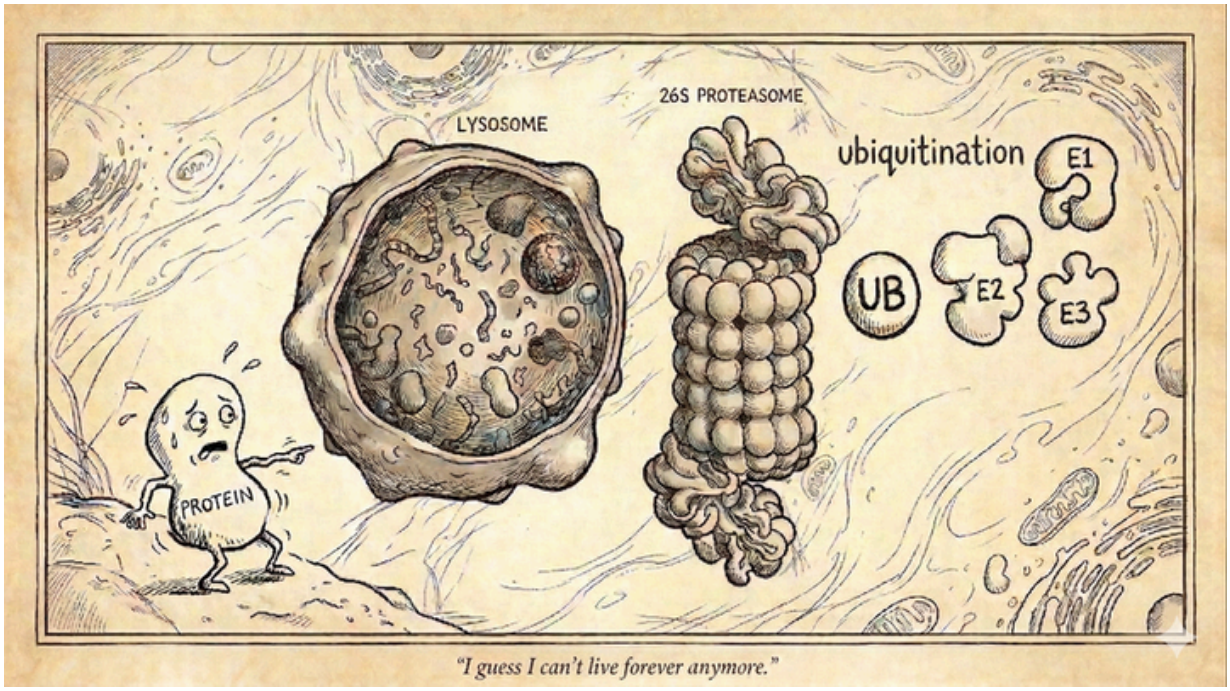
The reticulocyte turned out to be the ideal experimental system for discovering a second mechanism for the degradation of intracellular protein. Aaron Ciechanover, Avram Hershko, and Irwin Rose separated the proteins in reticulocyte lysates into two fractions. Fraction 1 contained proteins that did not bind the positively-charged resin, and fraction 2 contained those that did. Neither fraction alone could support degradation. Protein degradation was only seen when the two fractions were combined.[9] From these results, they gleaned that they were trying to elucidate a multi-component degradative pathway. There was no precedent for such a system.

The first fraction contained a small, heat-stable protein called APF-1, now known as ubiquitin.

Together, the three investigators made the astounding conceptual leap that ubiquitin was a protein that tagged other proteins for degradation. Using ubiquitin, they isolated the necessary components from the second fraction and showed that ubiquitin was transferred through three enzymes to be attached to a target protein in an ATP-dependent process.[10,11] For this groundbreaking work, Ciechanover, Hershko, and Rose shared the Nobel Prize in Chemistry in 2004.

The Protease

Ubiquitin was now known to mark proteins for destruction. But what was doing the destroying? In study after study, proteins tagged with ubiquitin would disappear. A protease was surmised, but difficult to find. When lysates were fractionated by size, the degradative activity was in the heaviest fractions. Because most enzymes are small, it was likely that the protein executioner was a massive multi-protein complex. In the early 1980s, electron microscopists had imaged large barrel-shaped particles, but did not know their function.[12] Around the same time, biochemists had isolated a very large complex with three



"I guess I can't live forever anymore."

distinct protease sites.[13] In 1988, Alfred Goldberg and Martin Rechsteiner independently demonstrated that the large barrels of unknown function and the very large complex with three distinct protease sites were actually one and the same.[14,15] This complex became known as the 20S proteasome. But identifying the 20S proteasome did not solve the mystery of how ubiquitinated proteins were degraded. Several groups showed that ATP was required to degrade a ubiquitinated protein. Alas, the 20S proteasome had no way to hydrolyze ATP. Its barrel was also closed at both ends, raising the question of how proteins gained access to the interior proteases. Goldberg showed that a cap — eventually called the 19S particle — sits atop the 20S proteasome and hydrolyzes ATP.[16] He proposed that the 19S particle unfolded a protein and translocated it into the 20S for degradation.[17] Two decades later, cryo-electron microscopy studies captured 26S proteasomes in the act of degrading a ubiquitinated protein, confirming the model.[18] At last, the fundamentals of ubiquitin-dependent protein degradation were understood — from the enzymes that condemn a protein to destruction to the executioner that carries out the sentence.

Worth remembering

This history reveals several enduring lessons. First, persistence through skepticism pays off — Schoenheimer's radical ideas about turnover faced decades of resistance, yet they reshaped biology. Second, serendipity favors the prepared mind — de Duve discovered lysosomes while trying to figure out the effects of insulin. Finally, every answer can reveal the next question. Each breakthrough in this story exposed deeper puzzles about regulation and mechanism. Embrace anomalies, trust your data, and remember that opportunities may be hidden in the problems that everyone else considers solved.

About the author

Jordan VerPlank is an Assistant Professor in the Department of Anatomy, Physiology, and Genetics. He studies intracellular protein breakdown and how activating the degradation of specific proteins can treat proteotoxic diseases.

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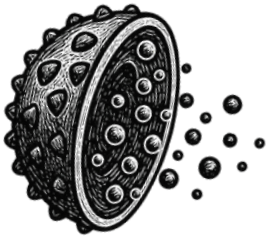
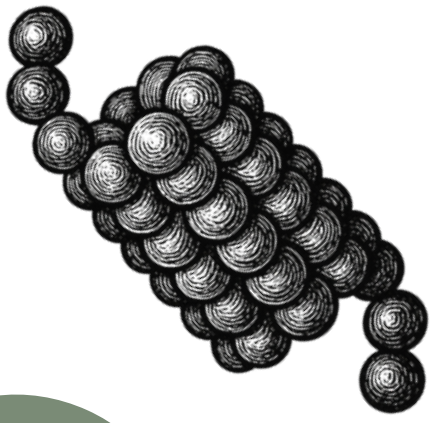


When Proteins Became Not-So-Permanent



A CALL FOR MODERNIZATION OF SLEEP AND CIRCADIAN MEDICINE TO ENSURE NATIONAL SECURITY

By CDR Kent Werner, MD PhD

Despite our technological advances, the most sophisticated weapon system in our military remains the human brain. Cognitive endurance, moral reasoning, inhibitory control, and rapid situational awareness are the currencies of the modern battlefield. However, a silent degradation of this asset is occurring through a systemic failure in the way we manage, diagnose, and treat sleep health. For decades, the medical community has relied on a low-resolution, crude method for analyzing and categorizing sleep physiological signals that has failed to prove useful in defining the features of restorative sleep. The 5-sleep stages – wake, N1, N2, N3, and REM – define our "sleep architecture" and are assigned based on the brain and muscle activity in 30-second epochs; yet they remain largely unchanged since their development in the 1950s. For example, if someone is found to have no rapid eye movement (REM) sleep, there is no diagnosis or clinical algorithm associated with that finding – despite a vast body of research that demonstrates benefits associated with REM. This lack of clinical enthusiasm for treating deficiencies in sleep architecture is likely derived from a lack of compelling clinical correlates for manipulating these stages, as the stages alone ultimately fail to correlate with important endpoints. While microfeatures such as spindles, slow waves, and REM atonia, are clinically vital, the traditional stages often fail to serve as meaningful predictors of health.

Vergun, D. [Defense Media Activity]. (2015 Nov 03). *EEG may Someday Boost Soldiers' Cognitive Ability* [Photo]. DVIDS.DVIDShub.net.

Furthermore, the circadian rhythm is practically ignored in most clinical and operational scenarios. A shift in the circadian rhythm can translate to opposing responses to light depending on an individual's phase-response-curve, potentially resulting in a significant reduction in performance. Currently, we lack facile tools to capture this critical biomarker in our clinics and operational scenarios. As physical sleep clinics close and referral networks become increasingly fragmented, the status quo has devolved into a degraded care pathway. To restore military readiness and protect the long-term health of our service members, we must pivot from this reactive, mechanical approach toward a framework defined by quantitative neuroscience and advanced signal processing.

The foundation of this shift begins with a nuanced understanding of current diagnosis and therapies. Positive Airway Pressure (PAP, e.g., continuous, or C-PAP) has long been heralded as the gold standard for treating sleep-disordered breathing, and for a specific subset of the population, its benefits are nothing short of transformative. When used consistently, PAP therapy significantly reduces cardiovascular disease burden and provides a critical defense against neurodegeneration. Research led by Dr. Andrew Varga at the Icahn School of Medicine at Mount Sinai, has illuminated the stakes of this intervention. Varga's work demonstrates that sleep fragmentation—the hallmark of untreated apnea—leads to an immediate rise in neurodegenerative proteins such as neurofilament light and tau within the blood.[1] These proteotoxic markers are associated with multiple neurodegenerative conditions, such as Alzheimer's disease. By stabilizing the airway and preventing hypoxia, PAP therapy reduces inflammation and allows for the preservation of sleep features such as slow-waves, which are associated with glymphatic waste clearance.

Other sleep links to neurodegenerative disease include recent data showing an association with PAP therapy and a reduced risk of Alzheimer's and Parkinson's disease progression with improved cognitive performance across the lifespan.[2] For the 20% of patients who enjoy using this therapy, the path to health is clear.[3] However, a grave error in medical and military strategy is the tendency to focus exclusively on this minority of success stories. We cannot continue to ignore the other 80% for whom the current solutions are intolerable or inaccessible. This is especially true within a military context, where suboptimal sleep is often accepted as a "badge of honor" (or simply an unavoidable fate) rather than recognized as a critical vulnerability.

For the Uniformed Services University, the link between sleep and national security must be viewed through the lens of human systems integration. Sleep is not merely a period of rest; it is the biological phase of maintenance. Chronic sleep deprivation mimics the cognitive impairment of alcohol intoxication, degrading executive function and increasing the probability of catastrophic error in high-stakes environments.[4] There is also a bidirectional link between sleep disorders and psychological trauma; failing to solve the sleep equation effectively hampers our ability to support our customers in the operational line.[5] The unmet challenges in sleep neuroscience also hamper our military treatment facilities' capabilities to treat the psychological wounds of war, such as PTSD. The current degradation of the sleep care pathway—characterized by the closing of specialized clinics in favor of automated, unmonitored referrals—is a direct threat to the resilience of the force. While efforts are underway to re-bolster these resources, a paradigm shift is needed to modernize the clinical diagnosis, treatment, and monitoring pathways. This modernization, moving away from traditional in-house sleep studies requiring sleep technicians and

complex wiring, will likely rely on wearables for at-home sleep testing for data collection and novel algorithms for real-time risk identification and mitigation. To bridge this gap, we must look to the intersection of neuroscience and signal processing. The traditional metric of sleep health, the Apnea-Hypopnea Index, is a twentieth-century tool being used to solve twenty-first-century problems. It measures how many times a person stops breathing, but it tells us nothing about the quality of the brain's recovery or the integrity of its neural oscillations.[6] The path forward lies in the adoption of breakthrough approaches to deep learning, specifically the use of foundational models.

Recent work in the development of SleepGPT and SleepFM describes the utility of these transformative models. SleepGPT treats sleep staging and pathology as a sequence-modeling problem, applying the same principles that govern Large Language Models to the "grammar" of the human brain. By training on millions of hours of polysomnography, SleepGPT can identify subtle transitions and micro-arousals that manual scoring misses.[7] Similarly, SleepFM utilizes multimodal contrastive learning to integrate EEG, EKG, and respiratory data.[8] This foundational model has demonstrated the power to predict the future risk of over 130 health conditions, including myocardial infarction and dementia, with a high degree of accuracy. For the military scientist, these models offer a way to move from "snapshot" diagnostics to a longitudinal, predictive understanding of a service member's health trajectory.[7,8]

However, the true frontier of quantitative neuroscience may be found within the microstructure of sleep, which contains features such as thalamic sleep spindles and cortical slow oscillations. For example, in the theory of Active Systems Consolidation, the precise timing of these oscillations relative to each other reflects the efficacy of short-term memory transfer to long-term storage (as tested by memory recall), serving as a biomarker of memory performance and cognitive plasticity.[9] When these oscillations are coupled with millisecond precision, the brain is optimized for learning and recovery. When that coupling is "de-tuned"—as it often is in the presence of sleep apnea or neurodegenerative onset—memory retention collapses and cognitive fatigue sets in. This "coupling precision" may prove to be a more accurate metric of a warfighter's readiness than any simple measure of sleep duration or respiratory events. Interestingly, multiple investigators have shown that this spindle-slow wave coupling can be enhanced using various forms of noninvasive neuromodulation such as closed-loop acoustic stimulation (CLAS), and multiple clinical trials are underway.

Modernizing this field requires a call to action for a new generation of scientists and engineers. We need minds capable of designing high-fidelity edge computing systems that can run models like SleepGPT on-device in operational environments. We need engineers who can refine signal processing algorithms to detect "de-tuned" spindle coupling in real-time, providing an objective marker of diminishing cognitive resilience before a failure occurs. We must move away from a "degraded" status quo and toward a future where sleep is treated as a dynamic, measurable, and optimizable neurological state.

The transition to this new era of sleep medicine must be hopeful but urgent. We are not merely looking to "fix a snoring problem." We are looking to restore the health of the individual and the readiness of the nation. By leveraging the convergence of human performance, neuroscience, and digital health, we can ensure that our military remains the most cognitively capable force in the world. The suffering of the

average warfighter with poor sleep is not an inevitability; it is a design flaw that we now have the tools to correct. Through the application of foundational AI models and the precision of quantitative neuroscience, we can move past the limitations of the previous century and build a framework of health that truly serves every member of the force. This is the mission for the next generation of military scientists: to modernize the field that impacts every human life, every single night.

About the author

Kent Werner, MD, PhD, is an Associate Professor in the Department of Neurology and the Neuroscience Graduate Program. His research investigates the impact of traumatic brain injury on sleep physiology and cognitive performance.

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Uniform Transitions: Menopausal Health and Military Service

By Jill Brown, MD MPH
CAPT (R) USUHS

McClary, R. [30th Armored Brigade Combat Team]. (2009 Jun 11). *Soldier in Focus* [Photo]. DVIDS.DVIDShub.net.

Menopause is a universal experience of women as they age, with the mean age of natural menopause 51.4.[1] Menopause is defined by the cessation of menses for at least a year; however, hormonal changes leading up to menopause can begin several years earlier. These fluctuations result in an array of symptoms that affect quality of life and account for cardiometabolic changes with long term health impacts. Vasomotor symptoms (VMS), primarily hot flashes and night sweats, are the most recognized menopausal symptoms, experienced by up to 80% of women and lasting on average 7.4 years.[2] In addition to impacting quality of life, VMS have been associated with increased risk of coronary heart disease, stroke, subclinical atherosclerosis, hypertension, adverse lipid profiles, and insulin resistance.[3]

Additionally, metabolic, cardiovascular, and musculoskeletal changes that develop during the menopause transition, compounding age-related changes, have significant implications for chronic disease development and progression.[4] An array of other central nervous system symptoms that may be less clearly attributed to the menopause transition but significantly impact quality of life and work productivity also may develop during this time, including sleep disruption, mood changes, brain fog, and difficulty concentrating.[5]

The history of women in the military has set the stage for the menopause transition to be even more underappreciated in the Military Health System (MHS) than in the civilian sector, and military service women may have additional risk factors, such as military sexual trauma, combat exposure, and environmental exposures that may impact the menopause transition. Military policy traditionally has explicitly restricted the roles women can serve, negatively impacting their potential career trajectories.

Active-duty servicewomen continue to face additional hardships compared to their male counterparts.

The Women's Armed Services Integration Act of 1948,[6] for instance, restricted the number of women who could be promoted to leadership roles in part due to concerns that women eligible for senior positions would be at the age of the menopause transition, which could lead to making "irrational decisions."[7] Executive Order 10240, signed by President Harry Truman in 1951 and in effect through 1975, stipulated that service women were required to separate from military service for pregnancy, childbirth, and adoption.[8,9] The historic exclusion of women from the military, with systematic separation as they age, set the stage for the MHS to be unprepared to attend to women's health needs as they navigate the menopause transition.

Since 2016, female service members have been eligible for all military positions, and as of 2023, they represented 17.7% (n = 225,119) of the active military.[10] Yet, active-duty servicewomen continue to face additional hardships compared to their male counterparts, such as high rates of military sexual trauma and sexual harassment, and challenges meeting family planning and management needs, with consequently higher rates of leaving the military compared to men. Indeed, a 2020 Government Accountability Office report found that female service members are 28% more likely to separate from the military than male service members, the percentage rising with increasing rank.[11] Military-specific exposures may impact the menopause transition; for example, military sexual trauma has been shown to increase the likelihood of severe menopausal symptoms[12] and recently published data indicate that Gulf War veterans with probable post-traumatic stress disorders have a higher likelihood of early menopause.[13] It is unknown, however, how many women are experiencing the menopause transition while actively serving.

Menopausal hormone therapy (MHT) is the most effective modality to treat menopausal symptoms and is indicated for the prevention of osteoporosis,[14] yet MHT has not been widely prescribed since publication of the results of the Women's Health Initiative (WHI) study in 2002.[15,16] The WHI study was a large randomized controlled trial evaluating the effects of hormone therapy on cardiovascular disease risk in postmenopausal women. The study was stopped early after the data and safety monitoring board found increased risks of breast cancer, coronary heart disease, stroke, and pulmonary embolism in women receiving combined estrogen plus progestin therapy.[17] Following the release of these results, MHT prescriptions fell by 79%.[18] A generation of women experiencing the menopause transition was disregarded. However, re-evaluation of the WHI data, with specific consideration of age, menopause symptoms, and drug formulation, has shown a favorable risk-benefit profile for MHT in the treatment of VMS and prevention of bone loss for women who are within 10 years of their final menstrual period or less than age 60.[19] The tide is now turning for both the medical community and women experiencing menopause to recognize the importance of the menopause transition. Yet, lack of education and knowledge about menopause continues to be problematic, with surveys of perimenopausal and menopausal women in civilian populations indicating that 60% report a lack of education and knowledge about menopause.[20,21]

While there is no published literature on U.S. service members' menopause experience, British service members in the menopause transition report that associated physical changes make performing mandatory physical fitness assessments more difficult, and symptoms such as hot flashes, bloating, and weight gain, can affect their confidence and comfort, especially when wearing the military uniform.[22] In the workplace, these

service members report challenges such as cognitive effects, irritability, anxiety, and fears of underperforming or compromising safety in critical tasks or while in command. Furthermore, some service members report a perceived inability to compete fairly with male colleagues, leading them to consider changing roles or leaving the military. These service members, who access healthcare through primary care, report a lack of healthcare professional awareness in managing menopause, attribution of menopause symptoms to other causes such as depression or stress, and infrequent prescribing of MHT. Unpublished results from a qualitative study recently performed at USU indicate similar experiences amongst U.S. service members navigating the menopause transition.[23] Participants reported feeling dismissed by military clinicians, difficulty accessing menopause-related care, challenges performing their duties due to menopause symptoms, and challenges meeting body composition and physical fitness standards impacting career progression.

There are likely multiple potential barriers to effective menopause management for military members, including healthcare professionals' comfort in managing menopause, access to menopause-related care, and patient education. Similar challenges and inequities exist in civilian menopause care; however, military-specific operational roles and stigma associated with performance in male-dominated fields adds an additional burden for service members seeking care for menopause-related symptoms.

While we are beginning to expand our knowledge about menopause in women service members and veterans, there is much more to be done. Women in the menopause transition are no longer actively excluded from service; rather, they are a vital part of our military, and we must prioritize their health and well-being. Initial steps to support women service members and veterans navigating the menopause transition may include implementing standardized menopause screenings, providing menopause training to military primary care clinicians, and updating policies to support those navigating symptoms while in operational settings. Greater understanding of the physiologic changes and needs surrounding the menopause transition, whether through clinical and translational research or policy changes, will directly affect combat readiness and retention of our most senior female leaders.

About the author

Dr. Jill Brown is a Professor in the Department of Gynecologic Surgery and Obstetrics. She is a general obstetrician/gynecologist and a Menopause Society Certified Practitioner. Her research focuses on women's reproductive health, including the menopause transition in military populations.

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Student Reviews

The student reviews section is written by both graduate and medical students completing their advanced degrees at USU. Topics cover areas of research on which these students are blossoming experts.

Examining Prenatal Care Access to Prevent Severe Birth Complications

By Teresa Russell

Maternal outcomes

For more than a decade, the United States (U.S.) has had the highest maternal mortality rate of any high-income nation (Figure 1).[1,2] In 2023, the U.S. maternal mortality rate was 16.6 per 100,000 mothers, which is nearly twice the 10 per 100,000 overall mortality rates and over three times the 5.15 per 100,000 (range 2.3-11.8) average mortality rate as compared across several high-income peer nations, like the United Kingdom and Canada.[2,3]

Most maternal deaths in the U.S. (80%) are preventable, caused by complications of labor and delivery that are not adequately managed.[4] The Centers for Disease Control and Prevention (CDC) created a composite metric called severe maternal morbidity (SMM) of severe complications during delivery admission that are associated with maternal mortality (Figure 2).[1,5–8] SMM is formally defined by the CDC as "unexpected outcomes of labor and delivery that can result in significant short- or long-term health consequences".[6] Indicators for SMM overlap with most of the common contributors to maternal mortality – such as cardiovascular conditions, amniotic fluid embolism, and anesthesia complications – highlighting the importance of SMM as an outcome.[5,8] Experts have referred to maternal mortality as "the tip of the iceberg", with SMM more common, more prevalent, and resulting in lifelong impacts to health and wellbeing when it does not result in maternal mortality.[9]

Characteristics affecting maternal health

The American College of Obstetrics and Gynecology (ACOG) defines social and structural determinants of health as including "historical, social, political, and economic forces, many of which are rooted in racism and inequality, that shape the relationship between environmental conditions and individual health."[10] These different social and structural determinants of health impact SMM risk, meaning the risk for SMM is not the same for every pregnant woman in the U.S. SMM disproportionately affects those under 18 or over 30 years as well as those who are of non-White race, Hispanic ethnicity, non-U.S. nativity, and unmarried, social determinants which have all been shown to significantly increase SMM risks.[11–14] Additionally, lower educational level, lower income quartile, not having private health insurance, living in large metropolitan or non-metropolitan areas, living in higher area deprivation index or medically underserved areas increased the risk of SMM.[11–16] Clinical risk factors – including hypertensive disorders, diabetes, obesity, mental health

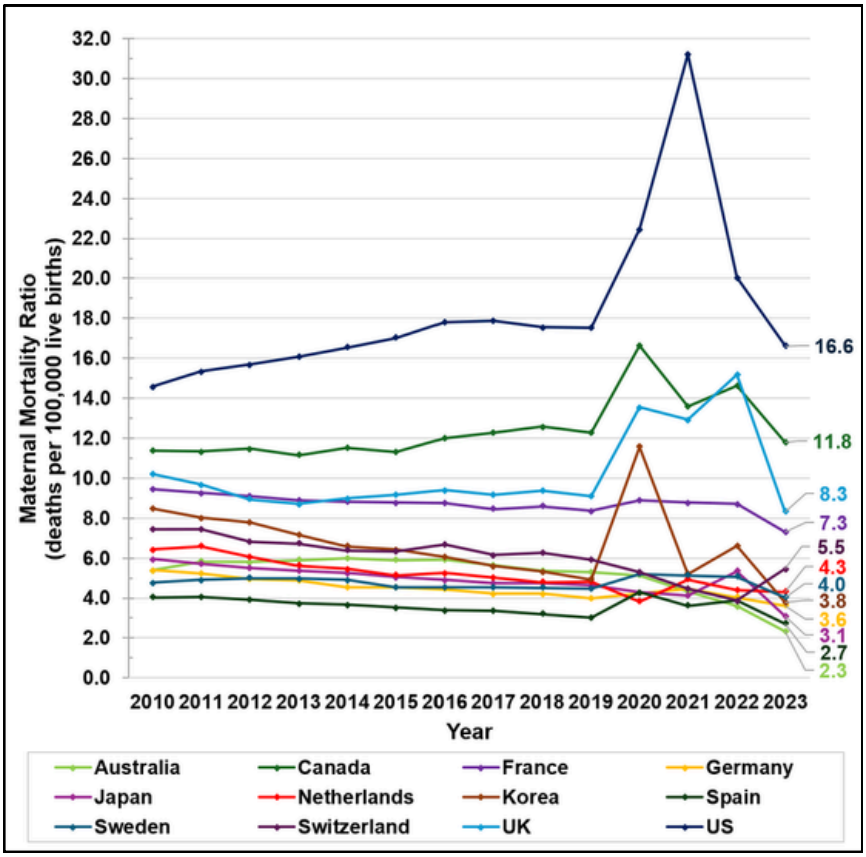


Figure 1. Maternal mortality ratios for the United States compared to peer countries 2010-2023. Data from the World Health Organization (WHO) Maternal Mortality Ratio Sustainable Development Goal measures.[41,42] The Maternal Mortality Ratio (MMR) is defined by the WHO as the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes.[42] MMR is measured as the number of maternal deaths meeting this definition in a specific time period per 100,000 live births during the same time period.[42]

Korea = Republic of Korea,
UK = United Kingdom,
US = United States

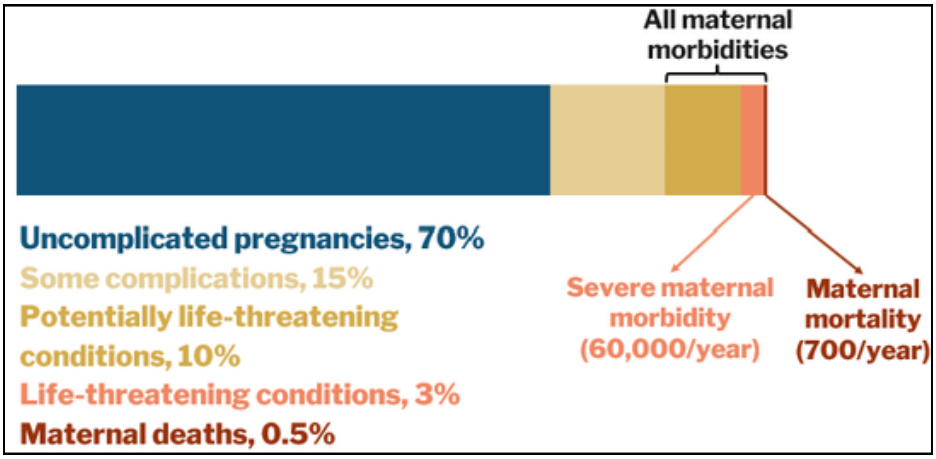


Figure 2. Relative rates and percentages of maternal complications during pregnancy. Adapted from Declercq & Zephryn, 2021.[7] This figure shows the scope of adverse maternal outcomes in the U.S. While 70% of U.S. pregnancies are uncomplicated, an important minority of complications lead to severe maternal morbidity (life-threatening complications with lasting impacts to health) and maternal mortality. Many of these complications are preventable or manageable and can be targeted to decrease maternal mortality.

disorders, and substance use – increase the risk of developing SMM at delivery and having more comorbidities further increases risk.[11,15–19] Obstetric risk factors – multiple prior pregnancies, delivery method, pregnancy with multiples, and prenatal care – also impact SMM risk.[12,15,16]

Prenatal care

Drivers of adverse maternal outcomes are multifaceted but one commonality among these outcomes is reduced access to prenatal health care.[4,20] This provides the opportunity for a preventive solution, since access to high-quality prenatal care from early pregnancy optimizes outcomes for both mother and infant.[21]

Prenatal care, or healthcare received during pregnancy from healthcare providers focused on optimizing health for both mother and baby throughout pregnancy, is the most frequently used healthcare service in the U.S.[21,22] Key features of prenatal care include 1) continuous risk assessment and identification, 2) coordinated

care for the prevention and management of pregnancy-related or co-morbid disease, 3) health promotion and education, and 4) psychosocial support from pre-pregnancy into the postpartum period.[22] ACOG recommends that pregnant women typically begin prenatal care in the first trimester, ideally by 10 weeks of gestation, then return every 4 weeks until 28 weeks, then every 2 weeks until 36 weeks, then every week until delivery.[22] This standard schedule has undergone little change since its establishment in 1930.[23] Less frequent or more frequent visits may be recommended depending upon individual risk factors, such as whether or not this is a woman's first pregnancy.[22]

The Kotelchuck Adequacy of Prenatal Care Index assesses prenatal care through 1) the initiation of services (when prenatal care began in the course of pregnancy) and 2) services received (how many prenatal care visits over the course of pregnancy) and provides a score based on the proportion of actual versus expected visits according to the typical ACOG-recommended schedule.[24] However, this scoring system will underestimate the adequacy of prenatal care for high-risk mothers as it is based upon recommendations for a low-risk, uncomplicated pregnancy and does not account for maternal risk factors.[24] While 98% of birthing women initiated regular prenatal care at some point during pregnancy in 2016, only 75.6% of them received adequate prenatal care or higher based on their Kotelchuck Adequacy of Prenatal Care Index scores.[24,25]

Forgoing or delaying prenatal care has been found to be more common among women with certain demographic characteristics (e.g., non-White race, Hispanic ethnicity, lower educational level, younger age, or public insurance), clinical risk factors (e.g. more pregnancies), health behaviors (e.g., unintended or mistimed pregnancy, no folic acid intake before or during pregnancy), and access to care issues (e.g., lack of a regular medical provider, transportation, and childcare).[19] These findings suggest that access to healthcare, likely stemming from adverse social and structural determinants of health, may be a key barrier to receipt of adequate prenatal care.

Emergency department use during pregnancy

When prenatal care is inadequate or inaccessible, women are more likely to turn to emergency departments for care during pregnancy.[26–29] Emergency department use during pregnancy stems from gaps in patient education or access to timely preventive services in a nonemergent setting - both of which should be encompassed in adequate prenatal care - or may indicate unmet clinical or psychosocial needs.[26,28–31] Furthermore, emergency department use during pregnancy, regardless of the reason for use, has been found to increase risk for SMM and other adverse maternal and infant health outcomes.[29–32] Additionally, emergency department care tends to be much more expensive than the average cost of care for comparable conditions in urgent care or outpatient settings.[33] Therefore, investigating emergency department use during pregnancy may lead to improved outcomes and decreased health care costs. Despite this, research on this topic remains limited.

Military relevance

Nearly half of TRICARE beneficiaries are women and approximately 100,000 births occur across the Military Health System (MHS) each year.[34] TRICARE is the Department of War (DOW) health benefit, which provides healthcare coverage to active-duty service members (ADSMs), retirees, survivors, and their eligible family members.[34,35] A third of these births occur at the 45 military hospitals providing inpatient care (32 in the U.S.), and roughly 40% of military

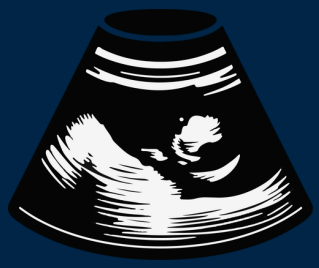
hospitalizations are for maternity and neonatal care.[34,36-38] Maternal health and outcomes among both active-duty and beneficiary women are key facets of military healthcare requiring dedicated attention.

Current gaps

Lack of national civilian and military-specific evidence: Little data is available on updated prevalence of SMM in the U.S. since 2015, so no studies have incorporated the COVID-19 time period, which greatly impacted access to care for everyone in the U.S.[39,40] No data on SMM prevalence across the entire MHS – including all deliveries in both the direct and private sector care settings – exists for any time period. Similarly, no study has examined the association between emergency department use and SMM in either a national civilian dataset or in the MHS. Current work is being conducted by Teresa Russell under Dr. Emily Ricotta at USU to try to fill these gaps.

Emergency department use as a proxy measure for access to prenatal care: Most studies examining access to prenatal care use surveys to measure initiation and frequency of prenatal care, which often lack rigorous clinical outcomes information and longitudinal follow-up of participants. Access to prenatal care remains difficult to measure using data sources like electronic health records and administrative billing data due to grouping of encounters making specific prenatal visit timing and frequency difficult to measure. Emergency department use during pregnancy could act as an indirect proxy measure for lack of access to adequate health care in the prenatal period that is more easily defined and examined within the confines of electronic health record billing codes.

Examining emergency room use during pregnancy and its effect on SMM could offer potential target areas for intervention to improve access to care, maternal outcomes, and care costs for both the U.S. civilian healthcare system and the MHS. Contrasting this relationship among the U.S. general population and those served by the MHS (with benefits equating to universal healthcare coverage) can specifically offer insight into the extent to which insurance coverage acts as a barrier to positive maternal outcomes. As insurance is the main avenue through which citizens of the U.S. access healthcare, this is invaluable insight to inform policy and improve the health of the public.



Finally, maternal healthcare and outcomes have widespread effects – not just on the birthing woman, but their infant(s), their family (e.g., partner, other children), their larger family system (e.g., their parents, siblings), and the community (e.g., co-workers, neighbors, friends) of which they are a part. In short, maternal health is public health.

About the Author

Teresa Russell, MS is a PhD candidate in Public Health in the Department of Preventive Medicine and Biostatistics at the Uniformed Services University of the Health Sciences who also works as a Research Associate II at the Henry M. Jackson Foundation for the Advancement of Military Medicine. At work, she currently supports the USUHS Consortium for Health Services Research's project on Fetal Alcohol Spectrum Disorders, focused on understanding and improving FASD care for children across the Military Health System. Her dissertation focuses on examining the effect of access to care – especially emergency department use during pregnancy – on severe maternal morbidity in both civilian and military-affiliated pregnant populations; her main advisor is Dr. Emily Ricotta.

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All the World's a Stage

The Critical Role of eIF2 in Regulating Translational Fidelity

By Megan Rasmussen

If a protein product is the finale performance of a massive stage production, translation initiation is the precise moment the curtain is raised. In every human cell, building proteins is an essential and highly controlled process with moving actors and props in this play. In this context, translation initiation is the "opening number" that sets the pace for the entire show and serves as the primary rate-limiting step for protein synthesis. Dysregulated protein synthesis has been implicated in many human diseases, including cancer and neurodegenerative disorders, and by understanding how we initiate this play, we can better understand these clinical conditions. The critical first step requires more than a dozen eukaryotic translation initiation factors (eIFs), including the essential eIF2. These factors act as stage managers to assemble the ribosomal machinery, or the cast and crew, ready with the show's props and full script. These factors ensure the synthesis of typical protein isoforms, meaning the "performance" follows the script perfectly. However, abnormal initiation results in the expression of atypical protein isoforms, essentially a chaotic, garbled version of the play where the crew misplaced the stage markers and the actors are in the wrong positions and follow the wrong cues. These "poor performances" in protein synthesis cause and promote disease progression. Therefore, the maintenance of strict or stringent translation initiation by eIF2, the lead stage manager, is required for cell health and function, and is essential for the show to go as planned.

For this show to begin, eIF2 must be in its "active" and functional state, which occurs when eIF2 is bound to an energy carrier known as GTP and the initial methionine, the starting amino acid, required for all protein synthesis (eIF2-GTP-initiator Met-tRNAiMet). Think of eIF2-GTP as the lead stage manager responsible for the lead actor (the initial methionine) and the cues required to start the opening act. The role of active eIF2 is to guide the lead performer to their starting mark on the stage, the canonical AUG start codon in an mRNA, with ribosomal props, like a 40S subunit, in hand. This ensures "high stringency fidelity," or perfect accuracy, for the start of the show (Fig. 1A).[1]

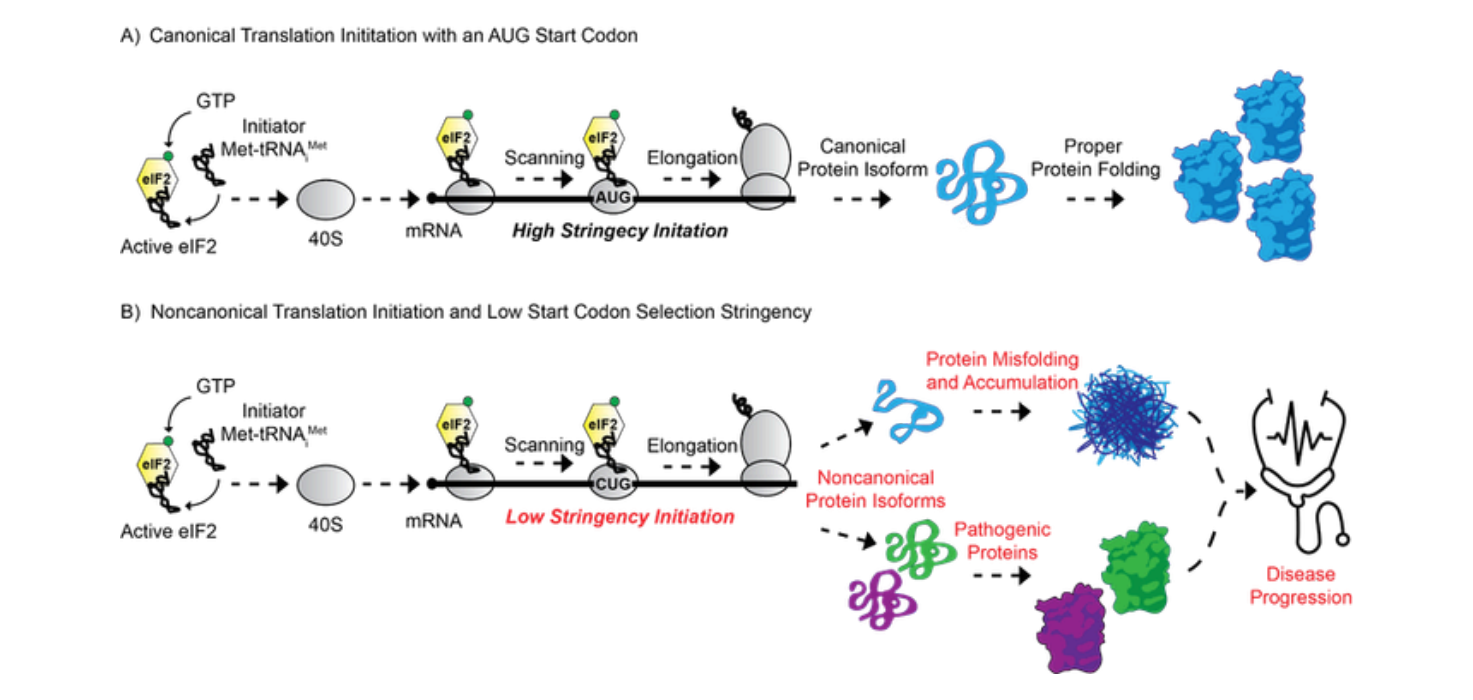

Figure 1: Schematic of the central role of eIF2 in maintaining translational fidelity by promoting canonical initiation at AUG start codons (A) and the biochemical and pathogenic consequences of impaired eIF2 activity and low start codon selection stringency (B).

Once the actor is confirmed to be in position, eIF2, lead stage manager, signals to the other stage managers or eIFs to cue for the curtain to rise, in which GTP hydrolysis occurs and its byproduct, eIF2-GDP, is released from the Met-tRNAiMet and 40S small ribosomal subunit.[2,3] eIF2 retreats to the wings of the stage to reset and starts to get ready for the performance the following night, or a new round of protein synthesis. This precise coordination, matching the actor to the AUG start codon and regulating the cue for the GTP hydrolysis, ensures the high fidelity required for a functional, canonical, or typical protein and a successful show.[2] With the actor starting their performance, the production can officially move into the next phase: elongation, where the rest of the cast joins the scene. The final act in this production is termination, when the last actor hits their last mark of the night, the translation stop codon. Some of the crew, or translation release factors (RFs), will bring down the curtain and put away all the props on stage when this final mark of the night is hit by the cast. These efforts by the crew will allow our lead stage manager, eIF2, to have all their props and cues ready to put on another flawless performance the following night.

Although canonical protein-coding sequences usually begin with an AUG start codon, eIF2 can occasionally initiate translation at noncanonical, near-cognate start codons (such as CUG, UUG, and GUG).[1] These "near duplicate" marks on the stage floor look remarkably similar to the real AUG start codon but are slightly out of place, resulting in a different protein isoform being synthesized. When the lead manager is unable to perform their duties exactly and get the actor to their designated AUG position, the performance struggles and fails to deliver the play that was promised, ultimately leading to a disjointed production and negative audience reviews. This is where my research comes in, understanding how eIF2 selects the correct AUG start codon.

Genetic Disease Models of Impaired Translation Start Codon Selection

Importantly, genetic variants or conditions that impact eIF2-GTP hydrolysis, the central mechanism that ensures high fidelity AUG start codon selection, can decrease the stringency of translation initiation and cause or contribute to disease pathogenicity.[4-6] For instance, a disease that I study, MEHMO Syndrome, is a rare developmental disorder in which disease variants impair translation initiation and decrease the fidelity of start codon selection.

The disease is characterized by a specific cluster of symptoms that form the MEHMO acronym: Mental (intellectual) disability, Epilepsy, Hypogonadism, Microcephaly, and Obesity. MEHMO is an X-linked recessive disorder, meaning the variant is carried on the X chromosome. Due to this inheritance pattern, the disorder primarily affects males. MEHMO results from variants within EIF2S3, the gene encodes the γ (gamma) subunit of eIF2. eIF2 is a protein complex made of three parts (α, β, and γ), and the γ subunit is the core component of the complex.[7,8] Mutated eIF2γ subunits can drastically affect where eIF2 initiates translation: at the correct AUG start codon vs. incorrect near-cognate start codons (e.g., UUG).

To explore the effect of disease variants on translation start codon selection stringency, we previously introduced paired AUG or near-cognate UUG reporters into wildtype and MEHMO variant yeast strains.[9] We observed a significant increase in initiation at the near-cognate UUG start codon in MEHMO variant strains as compared to their wildtype counterparts, emphasizing that MEHMO variants dysregulated protein synthesis by impairing start codon selection.[5,9]

Determining the full spectrum of mRNAs that are impacted by this low-fidelity translation initiation is a central focus of my research. To address this knowledge gap, we utilized patient cells expressing one of the most severe MEHMO variants, an eIF2γ frameshift (eIF2γ-fs) variant that results in a slightly shortened form of the eIF2γ protein. We performed Ribosome Profiling (Ribo-Seq), an unbiased, deep sequencing approach, in wild-type and patient-derived induced pluripotent stem cells (iPSCs). Ribo-Seq allows us to observe the differential translation of specific mRNAs between the eIF2γ-fs variant and the wildtype control. Gene Ontology analyses, a method of categorizing genes by their specific biological roles, have revealed alterations in the pathways critical for cell communication and ion signaling in the MEHMO variant iPSCs. Moving forward we plan to target these pathways for potential therapeutic intervention for the disease.

Cancer and Stress-Induced Loss of Translational Fidelity

Beyond genetic, disease-causing variants, a wide range of physiological conditions and factors can promote decreased start codon fidelity. For instance, oncogenic factors, including the cell-replication-promoting gene RAS, influence the expression of essential translation factors, ultimately causing increased initiation at near-cognate start codons in multiple cancer-related mRNAs (e.g. CTNNB1, Ki67, NRP1, RAC1, and FGF-2).[10,11] Using fibroblast growth factor 2 (FGF-2) as an example, studies with a rat bladder carcinoma model system have shown that impaired start codon fidelity and increased initiation at a near cognate start codon (CUG) in the FGF-2 mRNA produced a longer, N-terminally extended (24kD) FGF-2 protein isoform that localized exclusively to the nucleus, unlike the typical cytoplasmic (18kD) FGF-2

protein. The longer isoform of FGF-2 promoted tumorigenic properties and cell survival under conditions of hypoxia and low nutrient availability (i.e., cellular stress).[12,13] Additionally, when mice were subjected to intravenous injection of the 24kD FGF-2 protein isoform, extensive lung metastases spontaneously formed in ~25% of injections, compared to 2.6% in the mice injected with the 18kD FGF-2 protein isoform and 0.8% in negative control mice.[14] These results provide compelling evidence that low-fidelity translation initiation produces specific pathological protein isoforms that are sufficient to cause tumorigenesis in vivo and establishes impaired translational fidelity as a mechanism of cancer progression (Fig. 1B).[15,16]

Impaired Translation Initiation in Neurodegeneration

A low stringency translation landscape also becomes particularly damaging in the context of neurodegenerative disorders, such as Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD).[17] In these diseases, pathological expansion of short tandem repeats within non-coding regions of genes, most prominently the G4C2 repeat in the C9orf72 gene, reduces translation start codon selection stringency. These expanded nucleotide repeats undergo Repeat-Associated Non-AUG (RAN) translation, essentially generating toxic dipeptide repeat (DPR) proteins across all three mRNA reading frames without the requirement for a main canonical AUG start codon.[17,19] The emerging mechanisms suggest that these long, repetitive sequences fold into complex mRNA structures that cause the ribosome to stall or pause as it attempts to move along the mRNA genetic code. This stalling, combined with the cellular stress triggered by the expanded repeats, causes irregular initiation at incorrect translation start sites.[19] The production and accumulation of these toxic DPR proteins from RAN translation are now recognized as one of the core pathogenic mechanisms in ALS and FTD (Fig. 1B).[20]

Impaired Translational Fidelity as a Central Determinant of Human Disease

Together, these findings underscore that translational fidelity is highly sensitive to genetic, cellular, and environmental disruptions. eIF2 plays a main role in these conditions: when its activity is compromised, either through inherited gene variants, oncogenic rewiring, or chronic stress responses, the loss of start codon selection stringency reshapes the proteins synthesized in the proteome in ways that can drive diverse pathologies (Fig. 1B). From developmental disorders like MEHMO to cancer progression and neurodegeneration, impaired start codon selection emerges as a unifying molecular thread linking synthesis of aberrant protein isoforms and protein misfolding to disease. Thus, targeting the mechanisms that maintain translational fidelity represents a powerful, promising therapeutic strategy to restore translational accuracy and prevent the pathogenic shaping of the proteome across this wide spectrum of human disorders. Essentially, the show must go on and that's only possible when the cast and crew of the production are able to perform their roles. When just one member of the production is dysregulated, the whole performance can fall short and cost the playhouse good reviews. It's essential to get all members back on track so that cast, crew, and audience have a memorable and enjoyable theater experience from roll call to the final bows.

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About the Author

Megan Rasmussen is a fourth-year Molecular and Cell Biology PhD candidate in Dr. Sara Young-Baird's lab, studying the impact of dysregulated protein synthesis and its link to neurodegenerative disorders. Megan received her BS in Biomedical Sciences from the University of West Florida in Pensacola, Florida before moving to New Orleans to work as a lab technician at Tulane University. Outside of the lab, her interests include science policy and communication, where she hopes to pursue advocacy work focused on bridging the gap between scientific research institutions and federal policymakers.

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By Bradley Smith

The Reelin-Integrin Axis in Cortical Development and Degeneration

Forming upwards of 100 trillion connections within a volume smaller than that of a standard coffee pot, the human brain stands as the most complex biological structure known to science. Having undergone significant changes over the course of evolutionary development across species, the generation of the cerebral cortex is a process defined by the intricate orchestration of cellular division, identity, and migration. Corticogenesis of the mammalian neocortex establishes a six-layered architecture, a laminar arrangement that is evolutionarily distinct from the nuclear organization of the brain in birds and reptiles.[1] Cortical lamination, a term used to describe the layer-by-layer formation of the cortex, requires a developmental program capable of guiding billions of post-mitotic neurons from their birthplaces in the proliferative ventricular zones (VZ, **Figure 1**) to specific coordinates within the expanding brain surface or cortical plate (CP, **Figure 1**). Amid this complexity, the human brain is particularly staggering, with more extensive connections, greater cortical thickness, and gyrification (folding

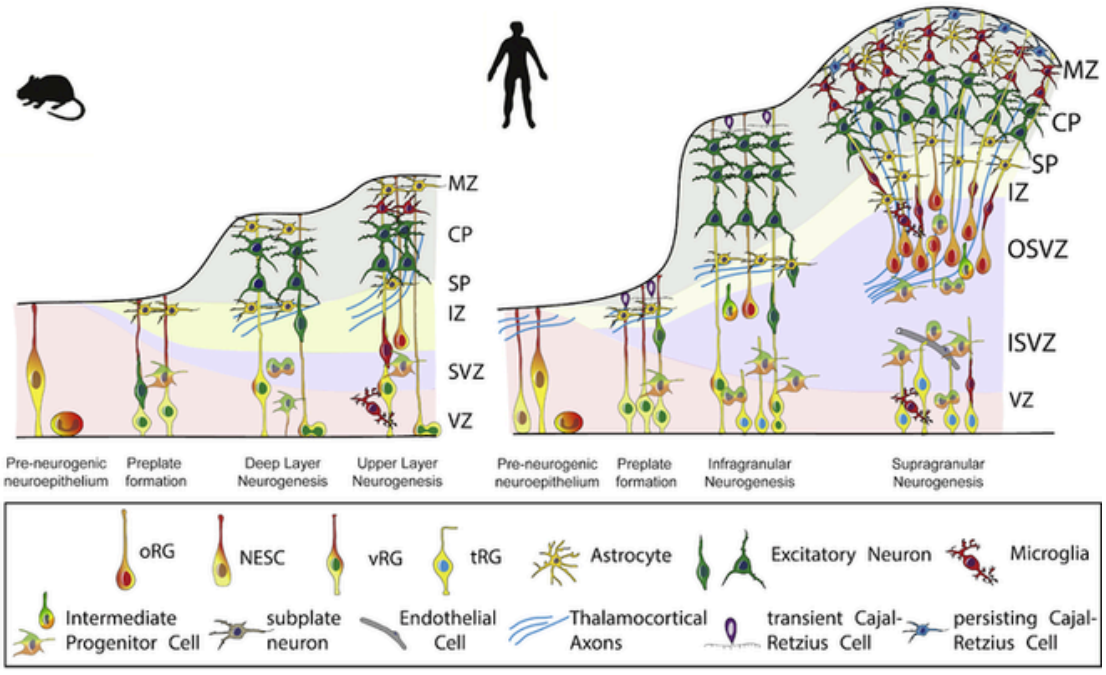

Figure 1. The developmental timeline of cell type proliferation in the developing brain, illustrating laminar neurodevelopment compared across humans and mice, depicting Reelin-secreting Cajal-Retzius cells and migrating immature neurons. The human cortex is far larger and more structurally convoluted than is the mouse cortex, reflecting a large difference in the amount of cells generated during neurodevelopment. Early-born neurons reside in the deeper layers of the cortex, while later-born neurons paradoxically migrate past formed layers of cortex and populate the superficial layers. *Abbreviations:* Outer Subventricular zone (OSVZ), Inner Subventricular zone (ISVZ), Ventricular Zone (VZ), Subventricular Zone (SVZ), Intermediate Zone (IZ), Subplate (SP), Cortical Plate (CP), Marginal Zone (MZ). Adapted from Cadwell et al.

of cortical tissue) than other mammalian brains.[2] What facilitated these evolutionary advancements is not fully clear, though it is evident that mammalian, and in particular, human neurodevelopmental programs require a careful, coordinated effort between cellular signaling and tissue biophysics.

Beyond its pertinence to the treatment of neurodevelopmental disorders, understanding neurodevelopment is of considerable interest for the study of brain tissue regeneration after injury and disease. The nature of acquired brain disorders is heterogeneous, ranging from focal traumatic lesions to the widespread cortical atrophy characteristic of Alzheimer's disease (AD). Efforts to remediate both acute tissue degeneration and progressive tissue atrophy have thus far proven unsuccessful, placing renewed importance on understanding the intersection between developmental paradigms and the molecular pathophysiology of degenerative brain disease. To develop a knowledge base for the regeneration of nervous tissue, an understanding of the mechanisms responsible for the development of the many-layered neocortex may prove useful.

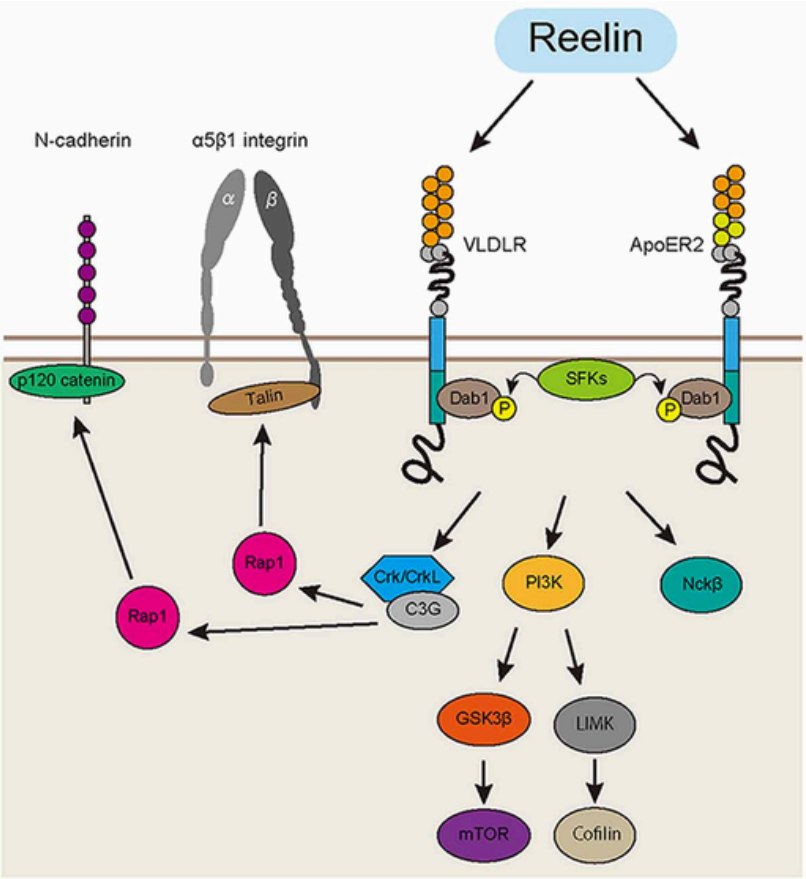

Figure 2. An abridged visual summary of intracellular Reelin signaling. Adapted from Ishii et al.[10]

Reelin: The Brain's Architect

The master architect of laminar neurodevelopment is a protein called Reelin, a large, extracellular matrix glycoprotein secreted by the pioneer Cajal-Retzius cells in the marginal zone of the cortex.[3] Reelin acts as the master regulator of cortical lamination by enforcing an "inside-out" pattern of neuronal layering. In this paradigm, early-born neurons settle in the deep layers (VI and V), while subsequently born neurons must migrate past their predecessors to populate more superficial layers (IV, III, and II).[4] This process requires migrating neurons to undergo a complex sequence of behaviors: attachment to ventricular radial glial (vRG) progenitor cells (**Figure 1**)[5], locomotion through the intermediate zone, detachment upon reaching the cortical plate, and terminal translocation to their final position.[6] Importantly, the human brain possesses Cajal-Retzius cells in greater number and complexity than the mouse brain, and the mammalian brain contains notably more of these cells than the non-mammalian brain.[7] The number of these cells correlates with the complexity of the neocortex, suggesting a critical role for Cajal-Retzius cells and Reelin in neocortical evolution.

Intracellular Reelin Signaling

Orchestrating neuronal positioning in a richly dynamic neurochemical and mechanical environment is a deceptively complex feat, yet is largely accomplished through Reelin concentration gradient-dependent signaling: increased Reelin

concentration promotes adhesion to the extracellular matrix (ECM) while simultaneously downregulating adhesion to the cellular (glial) guide (**Figure 2**).[8] The transduction of the extracellular Reelin signal into this complex cellular coordination requires a sophisticated and branching network of intracellular cascades. Canonical Reelin signaling is initiated by the binding of Reelin to two transmembrane receptors of the Low-Density Lipoprotein (LDL) receptor family: the Very Low-Density Lipoprotein Receptor (VLDLR) and the Apolipoprotein E Receptor 2 (ApoER2/LRP8). [9]

Reelin binds to VLDLR and ApoER2, inducing the clustering of these receptors on the neuronal surface and activating a variety of downstream mechanisms. Of particular interest are pathways involving Disabled-1 (Dab1), an adaptor protein which docks to the intracellular domains of VLDLR and ApoER2 receptors (**Figure 2**).[10,11] Dab1-dependent signaling cascades initiate the dynamic morphological and cytoskeletal rearrangements required for the execution of Reelin-dependent terminal translocation.

Among Dab-1's functions is to activate Rap1, a master regulator of integrins for cell adhesion. Specifically, Rap1 promotes the activation of integrin α5β1,[12] dramatically increasing the integrins' affinity for the ECM protein fibronectin which is predominantly expressed in the upper marginal zone. By activating Rap1, Reelin forces immature, migrating neurons to adhere strongly to the marginal zone by integrins, providing the traction required to pull the cell body up while simultaneously facilitating detachment from the radial glia. Reelin further orchestrates this process through inhibition of cofilin activity, promoting the stiffening of the actin meshwork in the leading process to provide anchoring to the marginal zone.[13] Reelin also interacts directly with integrins. Critically, migration along radial glial fibers is mediated by α3β1 binding to glia and the ECM component laminin, as well as gap junction adhesions. During terminal translocation, Reelin binding to α3β1 inhibits this adhesion, effectively unhooking the neuron from the glial rail.[14] This strong coordination of integrin mechanics positions Reelin as a master regulator of tissue biomechanics during neurodevelopment.

Brain Tissue Fluidity & Cell Migration

Interestingly, the fluid nature of the immature brain creates a much more permissive environment for these migrating neurons than does the mature brain.[15] Think of cells migrating through the immature brain as swimming through water, versus cells migrating in the mature brain swimming through maple syrup. Overall, however, human tissue is significantly more fluid and dynamic than that of mouse or non-human primate tissue, as indicated by exceptionally high nuclear motility and expanded intracellular spaces.[16]

The developing brain possesses viscoelastic properties, behaving as both a fluid and a solid.

With the fluid properties of the developing tissue allowing for greater cellular migration, higher Reelin concentrations would be needed to gain sufficient integrin-mediated pulling traction on softer substrate. This likely represents an underlying level of mechanical control which allows for greater cortical expansion in humans versus mice, and provides interesting mechanical context to the finding that mutations in the Reelin signaling pathways often present with more severe, disorganized migration phenotypes and nuanced phenotypic presentations in humans compared to rodent models.[17]

Indeed, higher tissue fluidity necessitates higher mechanical requirements for the establishment and initial maintenance of neuronal positioning. The developing brain possesses viscoelastic properties, behaving as both a fluid and a solid depending on the timescale and force applied.[18] Traction force microscopy (TFM) studies show that migrating neurons exert specific "pulling" forces on their substrate.[19] Within the various branching cascades initiated by Reelin, a considerable number are uniquely cytoskeletal in nature.[20] In the Reelin-centric process of terminal translocation, integrin-populated adhesions at the stiffened leading edge act as a "locking", or "pulling" mechanism. [6,8]

Relevant insights may therefore be generated through the synthesis of brain biomechanics and Reelin signaling biology. Reelin deficiency alters the viscoelasticity of the brain tissue, suggesting that Reelin-mediated adhesion may actually be responsible for the transition of the cortical tissue from a "fluid" aggregate of migrating cells to a "solid" laminated structure.[21] In this light, the Reelin-Integrin axis may effectively "cure" or solidify the developing neural tissue layer by layer. Intriguingly, one of the two known protective mutations for AD is a gain of function Reelin mutation, possibly suggesting that the cortical atrophy seen in AD is a manifestation of physical tissue delamination, which is countermanded by the enhanced adhesive signaling of neural cells with mutated Reelin. The mechanical failure of cell adhesion being a contributory factor in AD progression has been recently proposed, and also provides interesting context to the role of GSK3β.

The molecular mechanisms of laminar neuro-development are precisely calibrated to the mechanical properties of the developing brain. Accounting for the physical realities of the mature, injured, and/or diseased brain will provide crucial input for future efforts at treatment development, especially those concerned with the regeneration of neural tissue in adult patients through the manipulation of developmental paradigms, sensory mechanobiology, and tissue properties. By further understanding how Reelin interacts with intracellular signaling cascades and tissue mechanics to build the human brain, scientists may uncover deeper insights to our evolutionary past and overcome the paucity of treatments for neurodegenerative diseases.

About the Author
Bradley Smith is a third-year neuroscience PhD candidate in the labs of Dr. Barrington Burnett and Dr. Sharon Juliano. His research focuses on how blast overpressure affects the cellular anatomy of the central nervous system.

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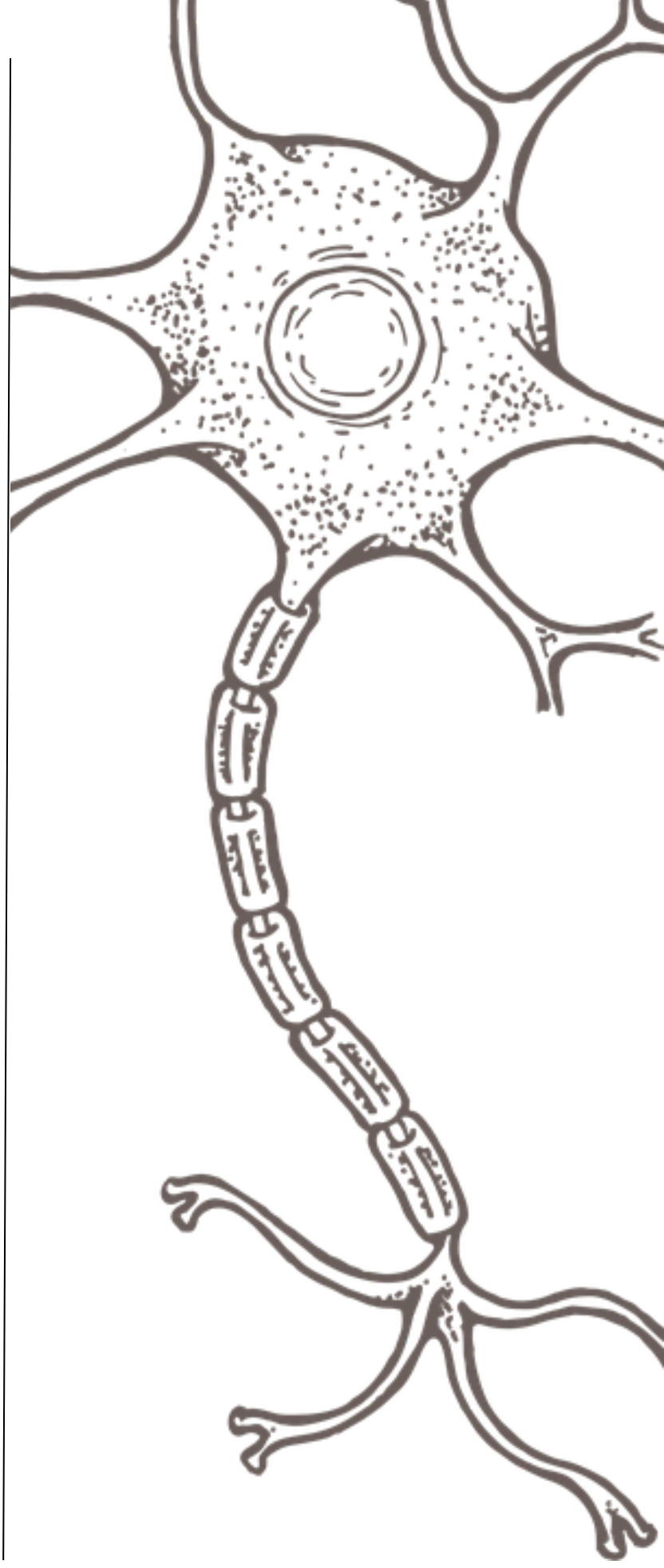

THE NEXT GENERATION OF AMPUTATION:

SURGICAL FRONTIERS FOR ENHANCED MOTOR DEXTERITY AND SENSORY RESTORATION

By 2LT Zachary Bailey

The experience of losing a limb extremity is often compounded by the realization that the clinically available prostheses fall short of patient desires.[1] Most conventional neuroprostheses rely on surface electrical signals from residual muscles to drive movement, a method frequently associated with difficulties in mastery and subsequent device abandonment.[2] While still effective for basic tasks, this residual muscle approach does not reflect how the nervous system naturally controls limbs. Furthermore, the sensory deficit is unaddressed by conventional myoelectric devices.[3] This lack of feedback is detrimental to native functionality, considering that upwards of 90% of upper limb peripheral nerve axons convey sensory information.[4] Multiple studies demonstrate an increase in dexterous control and enhanced functional performance of a prosthesis when sensory feedback is partially restored.[5-7]

To address these critical disparities and improve patient embodiment of the prosthetic limb, an improved, closed-loop system requires accurate transmission of multiple, independent efferent control signals while providing accurate afferent feedback back to the patient's nervous system.[8] The long-term success of such a bidirectional communication strategy depends intrinsically on the surgical strategy to optimize the residual limb for prosthetic-neural communication.[9,10]

This review focuses primarily on these surgical frontiers while also directing the reader to comprehensive reviews of implantable electrodes in advanced neuroprosthetic control and sensory feedback. It also serves as a reminder that military surgical practice must continue to learn, train, and improve these techniques, especially when not at war, so that we are best prepared to adapt to new injury patterns and higher case volumes if called upon.

SURGICAL FRONTIERS: OPTIMIZING THE BIOLOGICAL INTERFACE

Targeted Muscle Reinnervation (TMR)

TMR is a technique that reroutes residual, severed nerve endings from their original location to reinnervate intact muscles that have been denervated. This is done by coapting a nerve severed during amputation to a severed motor branch of a nerve that innervates a nearby intact muscle. The amputation-related nerve then regenerates along that motor branch and reinnervates the muscle (Fig. 1a,b).[13,14] This repurposes the muscle as a biological amplifier to generate electrical signals that improve prosthetic control by allowing users to move their prosthesis using natural movement intent.[15,16] Patients can now flex the wrist of their prosthetic limb by thinking of flexing the wrist of their phantom limb. This technique enables improved performance compared to myoelectric control that does not use native muscle-movement relationships.[17] This surgical technique has been employed in many clinical trials for neuroprostheses, but it has primarily gained clinical use for its pain prevention by reducing incidences of neuromas which are masses of disorganized axonal regeneration attempts at the free ends of large severed nerve bundles. Studies of acute TMR show that 92% of patients experienced no neuroma pain at follow-up.[15] TMR performed concurrently with amputation is associated with significantly lower odds of phantom limb pain (PLP) and residual limb pain (RLP).[20,21]

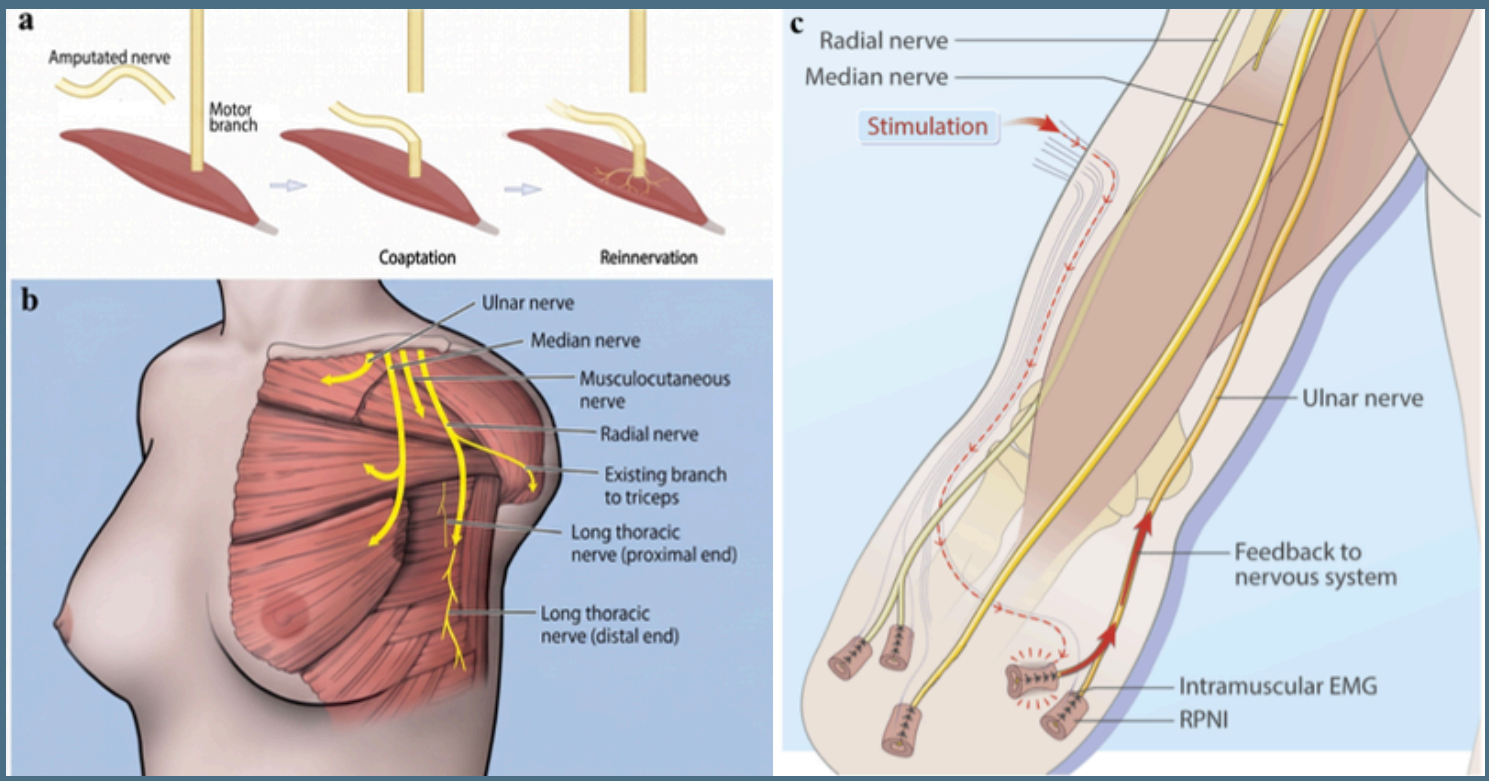

Figure 1. a) Schematic of TMR procedure in which an amputated nerve is redirected into an intact muscle by coapting to the previous nerve. b) Surgical plan of nerve redirection commonly used in a high transhumeral amputation.[13] c) Surgical plan of regenerative peripheral nerve interface (RPNI) placement in a transradial amputation with electrodes to show sensory feedback signal pathway.[12] Reproduced under the terms of a Creative Commons license.

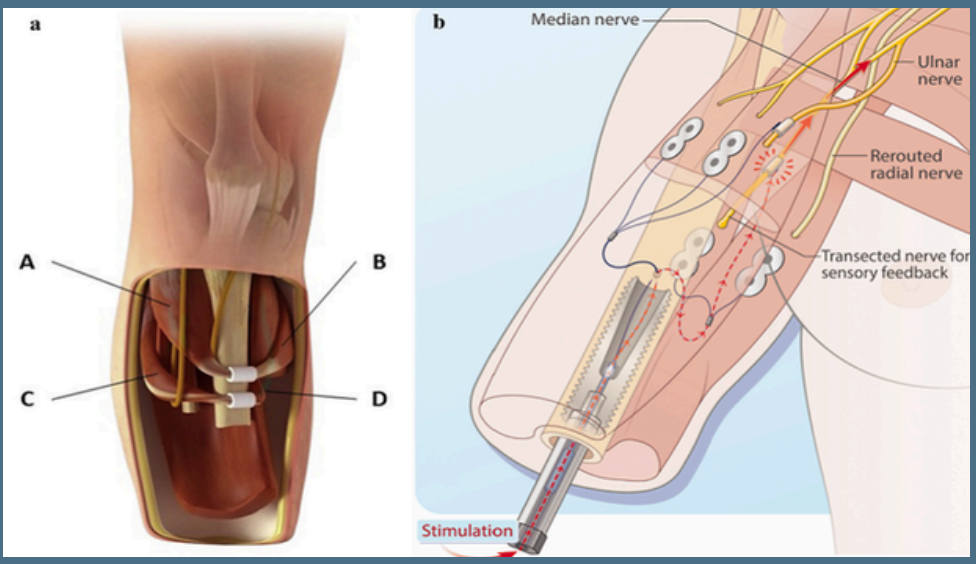

Figure 2. a) Surgical plan for a transtibial AMI procedure in which the agonist and antagonist muscles pairs are (A to B, C to D) attached through a synovial channel.[35] b) Osseointegrated implant in a transhumeral amputation. This implant also has electrode leads that enable transcutaneous bioelectronic communication.[12] Reproduced under the terms of a Creative Commons license.

Regenerative Peripheral Nerve Interfaces

The regenerative peripheral nerve interface (RPNI) is a surgical technique involving the implantation of a severed peripheral nerve into a free skeletal muscle graft, which gets wrapped around the new distal end of the nerve (Fig. 1c).[22] Over a period of 2 months, a regenerative process occurs in which both motor and sensory axons innervate the free muscle graft. This stable interface acts as a biological amplifier, turning small motor action potentials into larger, higher quality EMG signals.[23,24] This signal fidelity enables advanced control, including selective movement corresponding to particular muscles in the forearm in patients with transhumeral amputations.[25] Accurate sensory feedback has also been restored by stimulating RPNIs with implanted electrodes in a few patients, while still enabling effective motor control through the same RPNI and electrode construct.[26]

RPNIs also effectively inhibit neuroma - a painful nodule of nerve tissue - formation by promoting nerve regeneration and reducing neuroinflammation.[27] Both TMR and RPNI demonstrated similarly improved pain scores following neuroma resection in animal models, suggesting both are clinically feasible options for managing nerve pain[28]. A key distinction is that RPNI does not require the denervation of existing native muscles but rather uses smaller free grafts, preserving residual motor function while providing a stable, scalable interface.[29] Since RPNIs require neovascularization for the muscle grafts, they may not be appropriate for patients with active nicotine use or poor circulation, which both impair this process. This consideration is especially important in combat-injured patients with complex wounds. [30]

Agonist–Antagonist Myoneural Interface

The Agonist-Antagonist Myoneural Interface (AMI) is a reconstruction technique designed to preserve natural muscle pairing that normally controls joint movement using a tendon-to-tendon construct.[31,32] By surgically linking opposing muscles, AMI allows stretch and tension signals to be sent back to the brain, restoring an internal sense of position and movement, called proprioception.[33,34]

Clinical patient-reported outcome measures (PROMs) show that lower extremity AMI amputees demonstrated significant improvements across multiple physical and mental health domains 12 months post-amputation compared to their pre-operative state.[36] AMI preserves muscle function, resulting in significantly less muscle atrophy by physically linking the residual muscles together, compared to free muscle grafts that do not anchor to an antagonist muscle.[37]

Osseointegrated Neuromusculoskeletal Prostheses (OI)

Osseointegration involves anchoring a prosthetic limb directly to the bone using a metal implant. This eliminates the need for a socket and allows

mechanical forces to pass through the skeleton.[39] OI facilitates perceptive feedback directly through the bone, greatly improving prosthetic handling and stability compared to socket-based systems, which constantly shift on the residual limb.[40,41] However, the OI interface carries a higher risk of infection compared to traditional amputation techniques[40], but there are many ongoing efforts to reduce this rate.[42,43] The electric Osseointegrated Prostheses for the Rehabilitation of Amputees system (e-OPRA) leverages OI as an osseointegrated electronic communication gateway that allows routing of implanted electrode wires for motor control and haptic feedback through the transcutaneous abutment, so no wires are required to exit the skin in a secondary location.[44] Clinical results show that when sensory feedback was applied via nerve cuff electrodes within the e-OPRA system, coordination improvements were observed.[45] Furthermore, the resulting self-contained neuromusculoskeletal arm prosthesis showed stable functionality and intuitive, unsupervised daily use over several years.[46]

The Role of Implantable Electrodes in Surgical Success

The biological platforms established by the surgical techniques presented above rely on advances in implantable electrodes to achieve excellent restoration of function and long-term stability.[12] Nerve cuffs that wrap around the outside of peripheral nerves have demonstrated long-term biostability for up to 11 years in human implants.[50,51] However, extraneural cuffs can only isolate communication to the axons at the periphery of the nerve bundle. Penetrative electrode arrays circumvent this issue by putting multiple electrodes along a silicone shank and inserting it through the nerve bundle, so that there are electrodes equally spaced across the entire cross section of the nerve. However, they are more susceptible to an inflammatory foreign body response (FBR) that generates fibrosis due to small movement of the stiffer shank within the nerve, which causes chronic electrical instability.[52,53] Regenerative approaches are being explored to balance this selectivity and invasiveness tradeoff that is further explored in a review by Larson and Meng.[54]

Bridging Biological Variability with Intelligent Decoding

These various surgical procedures (TMR, RPNI, AMI) inherently create significant variability in residual neural anatomy and muscle targets across patients.[9,55] Anatomical variability will lead to highly variable biological signals across different patients. To effectively translate these independent biological signals into intuitive prosthetic control and localized sensory feedback, advanced decoding models, such as Recurrent Neural Networks (RNNs), may be necessary.[56] These decoding systems rely on machine learning algorithms to analyze post-surgical patient data and predict suitable personalized prosthetic configurations, but need to be further integrated with lightweight computer processing chips to handle large decoding models.[9]

Conclusion

No single surgical technique currently performs all the necessary functions for full motor control, sensory feedback, pain mitigation, and long-term stability on its own. The future of advanced amputation necessitates moving beyond working in functional silos to embrace integrated surgical strategies and post-operation rehabilitation. This complex network and the persistent risks of implantable devices necessitate realistic patient counseling. Continued scientific rigor is required to bridge the technology readiness gap and ensure that these innovations deliver sustainable function that improves patients' dexterity and sensory feedback. Finally, the military health system must stay abreast and engaged in these clinical translation efforts in partnership with civilian healthcare institutes to minimize the military readiness gap.

About the Author

Zachary Bailey is a 1st year Medical Student at USUHS, and a PhD Candidate in the Department of Bioengineering at Imperial College London, mentored by Prof Rylie Green. During his candidacy, he developed an implantable multi-electrode array that improved bidirectional peripheral nerve interfacing in pre-clinical models. These biohybrid surgical constructs could improve dextrous control and sensory feedback from neuroprosthetic limbs in patients with amputations. His broader research interests are in the co-development of surgical techniques and re-enabling technology.

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BREACHING THE BIOFILM FORTRESS

The Utilization of Glycoside Hydrolases to Combat Antibiotic Resistant Pathogens and Enhance Antibiotic Effectiveness

By 2LT Michael Ainsworth

Some of the most sophisticated defense systems on the planet don't involve blast shields and lasers, but are built by microscopic defenders to protect themselves from our most lethal attacks. That's the reality of a bacterial biofilm, a fortified, self-made bunker where dangerous, drug-resistant bugs lock themselves away to render our best antibiotics useless. For our warfighters with chronic combat wounds and for patients fighting hospital-acquired infections, these biofilm-generating bacteria are a persistent growing threat to health and recovery.[1,2] With the growing threat of antimicrobial resistance which claimed an estimated 500,000 lives in the US and Europe in 2014, experts suggest that this may rapidly increase to 10 million deaths per year by 2050, with costs surpassing $100 trillion worldwide.[3] These infections are often caused by a notorious group, composed of S. aureus, E. faecium, K. pneumoniae, A. baumannii, P. aeruginosa, and E. cloacae (ESKAPE pathogens). Our research proposes a novel weapon to crack this impermeable fortress: a family of enzymes called glycoside hydrolases (GHs).

The history of trauma medicine is largely defined by our arms race against bacterial colonization. During conflicts like World War I, minor shrapnel injuries or the rudimentary use of medical tubing routinely escalated into lethal sepsis, contributing to millions of preventable casualties.[4] The advent of sterile field dressings and the mass deployment of penicillin during World War II revolutionized this landscape, rapidly decreasing infection-related mortality and creating a false sense of medical supremacy.[5] Yet, while these historical breakthroughs successfully decimated free-floating pathogens, they failed to breach the bacterial fortress. Today, whether complicating modern combat wounds or colonizing routine hospital catheter lines, biofilms continue to drive chronic infections, serving as a stark reminder that our chemical arsenal still has a long way to go.[3]

Biofilms are complex bacterial communities in which the organisms are encased in a self-produced exopolymeric substance (EPS) matrix composed of proteins, extracellular DNA, lipids, and resilient polysaccharides. All of this together composes the stubbornly adhesive substance we call a biofilm.[6,7] This matrix is the key to the biofilm defense, making the bacteria within it up to 1000-fold more tolerant to antibiotics and the body's own immune system.[7,8] Traditional treatments struggle to

penetrate this physical barrier, and the ever-present danger of multidrug resistance (MDR) among ESKAPE pathogens only escalates the problem.[9-11]

Our study explored the potential of GHs, enzymes naturally produced by bacteria and fungus to break down polysaccharide chains and lead to controlled dispersal of portions of biofilms.[7,12] While our previous work has looked at their ability to disperse mature biofilms, this study tested their ability to work as prophylactic agents to prevent the establishment of the bacteria in the first place, either by interfering with the bacterial attachment to wound or device surfaces, initial microcolony biofilm formation, or complex biofilm maturation.[6] While each step along this biofilm development pathway can be targeted by our enzymes, we hypothesize that their use will interact with each stage to varying degrees, particularly during biofilm maturation. By impeding the formation of the mature biofilm stage, the defenses will be left incomplete when antibacterial treatment ensues, leaving the bacteria within exposed to attack. We focused on the two strains, or genetically identical variants, of each of the ESKAPE pathogens due to their prevalence as biofilm forming pathogens and resistance in combat and hospital settings.[2,13] In our initial experiments, we pitted various GHs against single-species biofilms. The results were encouraging but underscored the subtle complexity of the biofilm world. We quantified the results in two main ways: by measuring the total biomass (the cell abundance, EPS, and debris) and the number of live bacteria (Colony Forming Units, or CFU) within the biofilm.

We found that specific GH enzymes, particularly amyloglucosidase and pectinase from a fungus species of Rhizopus, were effective prophylactic agents, significantly reducing the amount of biomass in at least one strain each from five of the seven species tested. Intriguingly, the amount of biomass did not always correlate with the number of live bacteria, indicating that the enzymes were primarily dismantling the structural components rather than removing the cells themselves. Interestingly, another enzyme, α-amylase (A. oryzae), showed a more varied effect, reducing biomass in some strains while paradoxically increasing biofilm formation in others.

The most critical finding emerged when we combined the GHs with therapeutic antibiotics. If we could use

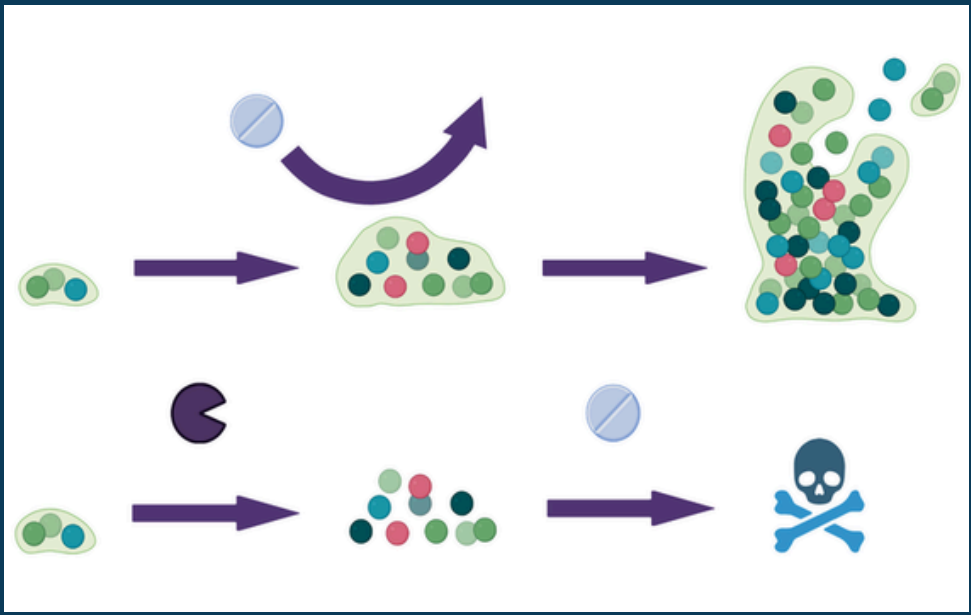

Figure 1. When bacteria (represented by the circles) aggregate, they form a protective, sticky layer around them, called a biofilm (light green). Bacteria form this biofilm by secreting proteins and other molecules. This biofilm prevents antibiotic medicines from reaching the bacteria and allows the bacteria to continue growing. Eventually, the bacterial colony grows big enough and smaller colonies break off and spread to other areas of the body.

an enzyme to weaken or destroy the biofilm's polysaccharide matrix, we clear a path for the antibiotics to reach the embedded bacteria. For E. faecium, S.aureus, and K. pneumoniae, the prophylactic application of GHs selected for their biomass-reducing prowess significantly boosted the effectiveness of the follow-on antibiotic treatment. For example, in both S. aureus and E. faecium, the combination of pectinase (Rhizopus sp) prophylaxis and daptomycin significantly reduced the bacterial load with one strain being reduced below our limit of detection (100 CFU/mL).

Similarly, combining amyloglucosidase (Rhizopus sp) prophylaxis with gentamicin drastically reduced K. pneumoniae below the limit of detection in one strain. This phenomenon suggests that the reduction in the physical, stainable biomass is the crucial step that allows the antimicrobial agents to penetrate the barrier and kill the bacteria.[17] The GHs act as an engineering crew, dismantling the defensive walls, while the antibiotics act as the strike force.

In clinical wounds, infections are rarely caused by a single species. Polymicrobial biofilms, in which multiple bacterial species coexist within a single biofilm, present an even tougher challenge. When we introduced the most promising GHs to these mixed-species cultures, the biofilms showed increased resilience, meaning the GHs alone were less effective at preventing their formation than in our single-species testing. These findings suggest that currently unidentified cooperative protective mechanisms may allow one species' matrix components to shield another.

Our research suggests a powerful new strategy against drug-resistant biofilm infections. By utilizing glycoside hydrolases as a prophylactic agent, applied either to wounds or to medical devices, we can actively prevent the formation and maturation of the biofilm defenses. The key lies in inhibiting the formation of the EPS matrix, which then sensitizes the bacteria to currently utilized antimicrobial strike forces. This dual approach could be highly valuable for military medics at the point of injury in a combat zone or for hospital staff trying to prevent common and catastrophic nosocomial (hospital-acquired) infections in catheter lines or wound dressings. This study lays the groundwork for future in vivo research to validate the use of GHs in clinical applications like wound packing materials or in-line locks to prevent chronic and persistent infections, ultimately offering a strategy to dismantle the bacterial entrenchment and preserve the fighting strength of our personnel.

About the Author

Michael Ainsworth is a fourth-year M.D./Ph.D. candidate under the mentorship of Dr. Kristi Frank. His current research focuses on novel enzyme therapies to disrupt bacterial biofilms and preserve antibiotic effectiveness in clinical and battlefield medicine.

AI Statement: The author acknowledges the use of Google Gemini (accessed February 2026) to suggest a title that draws attention and includes the necessary information. All AI-generated suggestions were reviewed, revised, and approved by the author, who takes full responsibility for the accuracy and integrity of the work.

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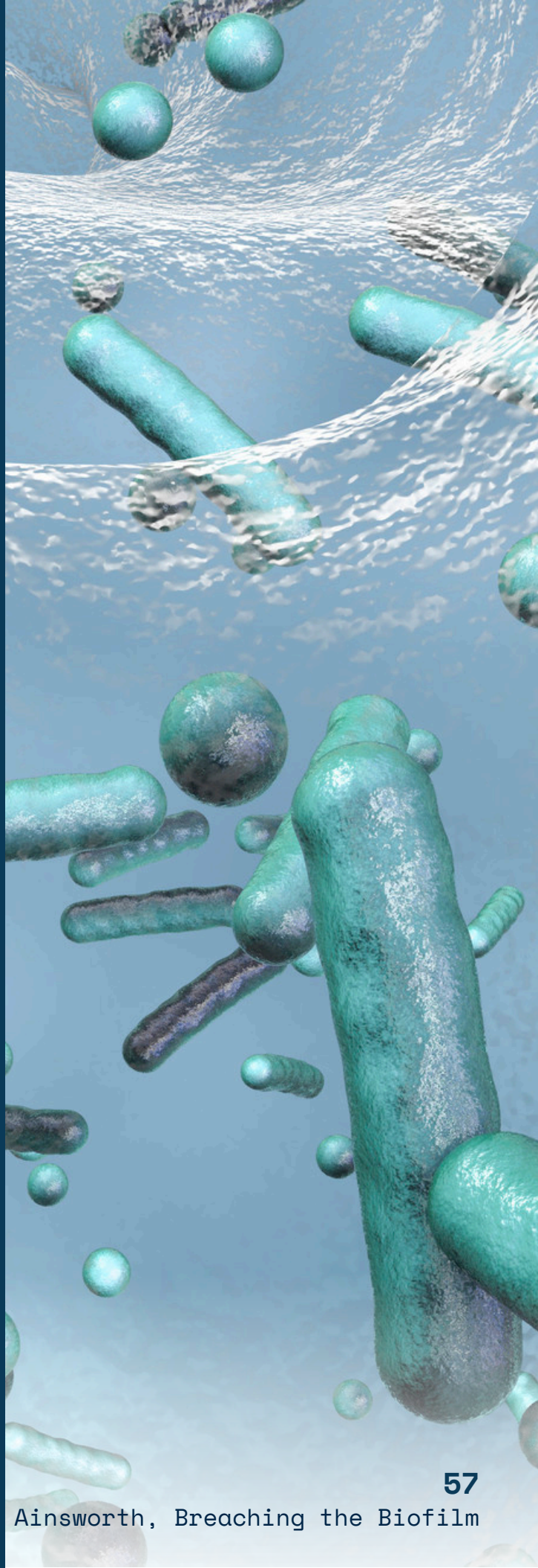

Clinical Corner

In this section, our USU Science Review Clinical Team has interviewed expert clinical faculty at USU. Join them as we hear about their professional journey in clinical practice and research.

Moving the Needle on Military Injuries

Authors: 2LTs Jason Lee, Jenova Kempkes, Srija Seenivasan

What threat to military readiness costs $3.7 billion annually and has increased disability discharges by 13x from 1981 to 2005?[1,2] Did you guess musculoskeletal injury (MSKI)?

Despite the widespread and growing problem of MSKIs on the fighting force, few military treatment facilities (MTFs) have the infrastructure to research MSKI treatment and preventative care. The Musculoskeletal Injury Rehabilitation Research for Operational Readiness (MIRROR) program, headquartered at Uniformed Services University (USU), was created to fill this very gap through surveillance, multisite clinical trials, and implementation research focused on MSKI care. Dr. Xiaoning "Jenny" Yuan, MD, PhD, a biomedical engineer turned physiatrist, directs MIRROR.

She also serves as the Vice Chair for Research and Associate Professor in the Department of Neurology and Rehabilitation Medicine (NRM) at USU. Her work has spanned benchtop tissue engineering to population-level research, tracking millions of healthcare encounters, and interventional orthobiologic studies with a common goal: restoring and preserving function for service members.[3]

USU Science Review (USUSR) spoke with Dr. Yuan about her mentors who nudged her toward the physician-scientist career, how she found PM&R in the middle of her PhD, what it means to run a large collaboration like MIRROR, and where she sees the most fruitful pathways for regenerative therapeutics to realistically "move the needle" on readiness.

USUSR: Your path combines engineering, bench science, and clinical medicine, beginning with your biomedical engineering undergraduate at Duke to your MD-PhD at Columbia, to clinical PM&R at New York Presbyterian. Now you are helping lead the military musculoskeletal research as Vice Chair for Research in PM&R at USU. How did the experiences across these different domains shape your approach to the problem of musculoskeletal injury, and what drew you to focus this expertise on military populations?

JY: When you look at someone's CV, it's easy to think there was a very intentional plan, but I did not start out thinking I was going into medicine at all. As a kid, I thought I'd do astrophysics or genetics. Medicine only came into the picture after several high school and college internships, including four summers at NIH. I found my footing in a lab working on mesenchymal stem cells for tissue engineering of cartilage and meniscus, and a mentor there suggested an MD/PhD. That was really the decision point.

Midway through my PhD, I discovered PM&R, a specialty that grew out of wartime and is dedicated to restoring function after injury. Hearing the Columbia University PM&R chair describe it, I felt like it was the clinical version of what I was already trying to do in a petri dish. My move into military medicine was more serendipitous than planned. At a conference during Sports Medicine fellowship, I happened to sit next to the vice chair of PM&R at USU, and that opened the door to USU.

Image: Dr. Jenny Yuan, MD, PhD

The gap between what is elegant in the lab and what is actually deliverable to a patient is real, though not insurmountable, and that is exactly why the clinician-researcher relationship matters so much.

USUSR: I imagine going from lots of time spent in the lab to running large-scale surveillance studies can feel like quite the jump. How have your initial research goals changed from when you started your MD-PhD, and how do you think about your bench skills now?

JY: I haven't worked full-time in the lab in over ten years, and I am at peace with that. After about fifteen years across high school, college, PhD, and residency electives, I gradually realized that my strength was not being the most creative bench scientist. It was understanding both worlds and being able to translate between clinicians and researchers, which not everyone wants or is positioned to do. That said, the PhD gave me something irreplaceable in terms of how to follow through, troubleshoot, and make contingency plans when something isn't going the way you expect. I tried to design my PhD work around clinical relevance, and almost as soon as I was back on clinical rotations, I quickly saw where my assumptions broke down, particularly around cell-based therapies. The gap between what is elegant in the lab and what is actually deliverable to a patient is real, though not insurmountable, and that is exactly why the clinician-researcher relationship matters so much.

USUSR: MIRROR now supports dozens of MSKI studies across the Military Health System. From the inside, what does that infrastructure actually look like, and how did you and your collaborators build it out?

JY: MIRROR was intentionally set up as a collaboratory, as an infrastructure to support PIs doing MSKI research across the Military Health System. I may be the director of MIRROR, but I am far from the only PI supported by MIRROR. Because military personnel move every few years, clinicians interested in research often lack the support to navigate the complex process that is research within the MHS, and MIRROR fills that gap with program management, regulatory support, data analytics, and local know-how at study sites. Practically, that sometimes means walking an active-duty clinician through setting up an IRB account, getting the required agreements in place, running recruitment, and then supporting analysis and manuscripts, the kind of scaffolding you might take for granted at a large academic center but that does not exist at every MTF. We are intentionally not service-specific. We work across all branches and with many partners, and we try to build economies of scale through our infrastructure, so that every site is not starting from scratch on its own.

Dr. Jenny Yuan speaking at the Extremity War Injuries XVIII Symposium.

USUSR: How do the injury surveillance work and your regenerative meniscus/hydrogel work connect in your mind?

JY: The connection is somewhat loose, but if you think about the goal of military medicine, it is really about readiness and rapid return to duty. The surveillance work establishes where we are right now, and the regenerative strategies are about where we could go. When you think about modern threats, longer time on the battlefield, and limited ability to evacuate injured service members, you can imagine scenarios where surgery is simply not an option. In those cases the full spectrum of interventions matters, from self-management apps that do not require Wi-Fi to dry needling and shockwave to ultrasound-guided injections that could be made available at earlier roles of care, all the way to future cell-based therapies for injuries that would otherwise require surgery and a long recovery. I have always been a bit of a jack of all trades, and I am genuinely interested in anything along that spectrum that can help restore function, because in PM&R, we really do think about the individual person in front of us, and if something works for that person, that is enough.

USUSR: MIRROR has helped lead the first population-level assessment of MSKI burden specific to female service members. What have we learned so far, and where do you hope this line of research will go?

JY: Together with our collaborators, we have shown through population-level analyses that active-duty service women have higher risks and prevalence of MSKIs than men, with substantial healthcare utilization and real differences by service, including high prevalence in female soldiers and elevated relative risks in female Marines.[4] Those findings confirm this is a system-level pattern, not just an anecdote from one clinic. The next step is moving from documenting that burden to understanding why it exists, whether that is training practices, occupational roles, or biological and anatomical factors, and then figuring out what we can actually change. Across MIRROR, I am also excited about work that plays to my clinical strengths, like ultrasound-guided diagnostics and training other providers to use ultrasound for rapid assessment, alongside regenerative work like an upcoming FDA-regulated study for Achilles tendinopathy with the Department of Medicine at USU. The goal of all of this is to make sure what we develop is not just something I can do at Walter Reed, but something useful and accessible to the broader group of clinical and non-clinical personnel who are out there caring for service members every day across all settings.

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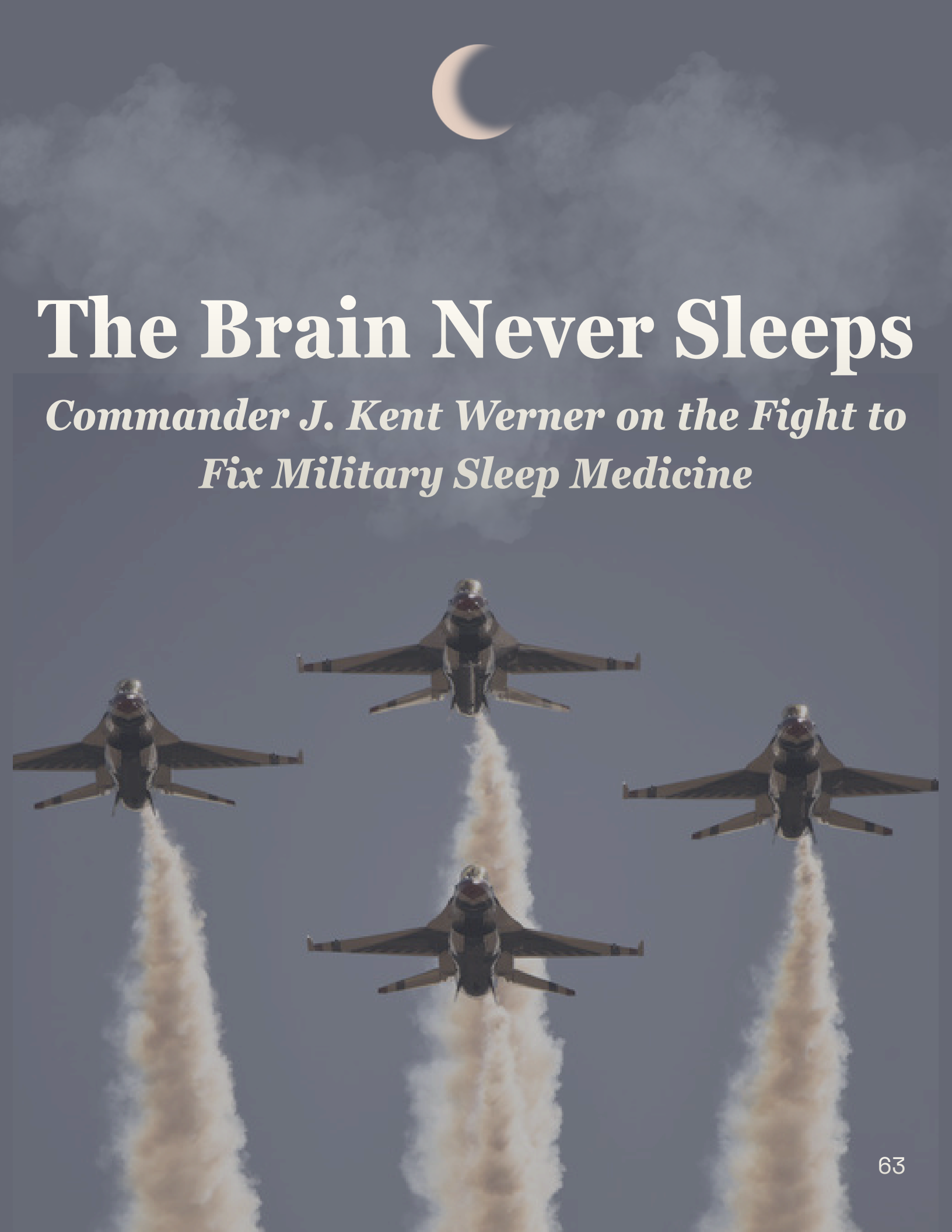


The Brain Never Sleeps

Commander J. Kent Werner on the Fight to Fix Military Sleep Medicine

Sleep deprivation affects between 27 and 38 percent of active-duty service members, impairing cognition at levels comparable to alcohol intoxication and directly threatening operational readiness. Despite this, sleep remains one of the most underfunded and structurally neglected areas of military medicine. Commander J. Kent Werner, MD, PhD, neurologist, sleep scientist, Navy officer, entrepreneur, and father has made it his mission to change that. As the director of the SWORD Lab at USU, the Navy's assistant specialty leader for sleep medicine, and the founder of the neuroscience startup Cogentis Therapeutics, he sits at a genuinely unusual intersection of bench science, clinical care, and military service. His research spans the glymphatic system, the role of CDK5 in neurodegeneration, and the electrophysiology of sleep, with a throughline that connects personal loss, serendipitous mentorship, and an almost stubborn determination to always ask the harder question.

USU Science Review (USUSR) spoke with Dr. Werner first about the childhood experiences that first drew him toward neuroscience and how a lab next door at Hopkins changed everything. He also reveals what it really takes to juggle a startup with active military service, and why he believes the DoW can do better to utilize its most powerful readiness tool: sleep science.

USUSR: You have had a genuinely unconventional path to where you are now. Can you tell us about your early life and how those experiences first drew you to science and to the military?

JKW: My father died when I was five from a rare throat cancer that would easily be cured today, and my mother was eventually diagnosed with schizophrenia. She took her own life when I was eleven, and I think even then, I was already asking why behaviors are what they are and wondering about the brain. After that I went to live with relatives and eventually ended up at a military boarding school for high school, which turned out to be a great experience. I became the cadet corps commander, really bought into the structure and independence it gave me, and from there found the Naval Academy, where I thought I would be a political science major and fly, but ended up falling in love with chemistry instead. I took a couple of internships, including one at the Naval Medical Research Center diving pigs and testing therapies for decompression sickness, and another at Lawrence Livermore studying radionuclides, and those experiences shifted me toward wanting to do real science. I changed from aviation to surface warfare knowing that path would make it easier to eventually transition to medicine, applied to Hopkins, got accepted off the waitlist, and they were generous enough to hold my spot indefinitely while I deployed on the USS Mahan to the Mediterranean, the Irish Sea, and the Caribbean. Those years on the ship, learning what it means to lead, to stand watch, and to be operationally sleep-deprived, shaped how I understand the patients I work with now more than almost anything else.

Image: CDR J. Kent Werner, MD, PhD

USUSR: And from Hopkins, you ended up in neurology and eventually sleep medicine. How did that happen, and what specifically pulled you into sleep?

JKW: At Hopkins, I became president of the neurosurgery interest group because I loved the idea of making an immediate, physical impact on a patient. I spent a lot of time in a neurosurgery research lab but then I discovered the lab next door run by Dr. Solomon Snyder (eponym of JHU Neuroscience department), who was one of the most creative scientists I have ever encountered.[1] He discovered gasotransmitters, which are gases like nitric oxide and hydrogen sulfide that act as neurotransmitters. He also discovered how caffeine works in the brain to keep us feeling energized. That was genuinely transformational for me. I eventually realized I found neurology's detective-like problem-solving more compelling than repeating medical procedures.

So I stayed at Hopkins for neurology training, and it was during residency that sleep grabbed me. What struck me was that during sleep you get a real, objective, high-resolution fingerprint of brain function through EEG that cuts through all the noise you see in a waking patient, and you can actually watch memories being laid down with EEG spikes and dips, which we call spindles and slow waves, in real time.

Then in 2013, the glymphatic system was described, which is this remarkable waste-clearance network in the brain that is roughly 90 percent more active during sleep, and which appears to be disrupted by traumatic brain injury and is closely tied to neurodegeneration.[2,3] I thought: here is a field full of low-hanging fruit, where the technology already exists to manipulate sleep physiology and it just has not made it to the clinic yet. The military relevance is obvious because the people I am trying to help are sleeping terribly, are getting TBIs, and are developing neurodegenerative conditions down the line.

USUSR: You also founded Cogentis Therapeutics around a CDK5-targeting peptide. What is the science behind that, and how do you manage running a startup while serving on active duty?

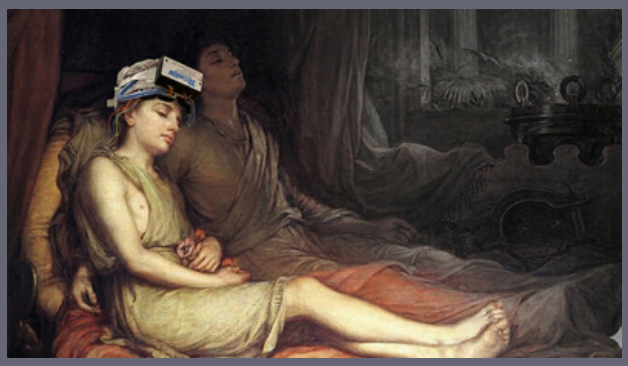
JKW: The startup came out of an NIH competition where they put their top intellectual property from NINDS up for teams to commercialize. I found a peptide developed by a brilliant NINDS scientist named Harish Pant targeting CDK5, a kinase that becomes overactive in almost every neurodegenerative process you can name, including Alzheimer's, ALS, frontotemporal dementia, and Parkinson's.[4] All of pharma had tried to drug it through classic enzymatic inhibition of the active site, but CDK5 has so many closely-related molecular cousins in the body that you end up with off-target toxicity, so the whole field effectively walked away from it. The peptide approach is different because it disrupts a specific protein-protein interaction rather than hitting the active site, which gives you far more molecular specificity, and that is what drew me to it. We ended up winning the elimination rounds over about a year and a half, licensed the compound, formed Cogentis, and we have now tested the peptide in six different neurodegeneration models. Managing that alongside active duty service comes down to firewalling time strictly. None of the company work happens on government time. I take leave when I need to attend anything work-related to the company. If you try to multitask across a startup, a lab, clinical duties, and a family, you are going to fail. You have to be multiplexing, meaning doing each thing fully during its dedicated time, and you have to be honest with yourself about when something is not working and let it go rather than dragging it forward out of obligation.

USUSR: You mentioned wanting to make changes in how the military handles sleep medicine. What does that actually look like in practice?

JKW: We published a paper showing that half of the narcolepsy diagnoses that tired service members received on the outside were overturned when they came back to see us. That is a symptom of a bigger problem, which is that we are spending more than twice as much outsourcing sleep care to civilian providers who are not incentivized to do the real work. They put people on CPAP (breathing device), order an MLST (sleep test), and move on, without ever looking at a sleep schedule or thinking carefully about circadian factors [the body's natural sleep cycles and rhythms]. Meanwhile, we are actually tearing down our internal sleep infrastructure rather than building it up, partly because hospital directors are rightly filling critical care and other deployability priority-related slots first, and sleep tends to get deprioritized. The DHA recently removed the word sleep from all of its research priorities in its psychological health and TBI funding calls, which I genuinely think is a mistake given how tightly sleep is linked to TBI recovery, cognitive performance, and readiness.[5] I have written a white (formal, evidence-based guidelines) paper on this with counterparts in the Army and Air Force that outlines a plan to modernize sleep medicine through a virtual sleep hub, automated algorithms, at-home monitoring, and bulk purchasing of devices, which we estimate could save millions of dollars per year that could then be redirected to strengthen our infrastructure and research capacity. The data on what sleep deprivation does to a warfighter is not ambiguous. Impairment from inadequate sleep has been shown to be comparable to alcohol intoxication, and it significantly increases injury risk. I am optimistic leadership will respond once they see the full picture, especially the part about saving money.

USUSR: If you could build the Kent Werner Center from scratch, what would its mission be, and where do you see your work going from here?

JKW: The core mission would not look that different



Somnus, the Roman god of sleep, reimagined with an fNIRS device for functional brain imaging during sleep.

from what I am doing now, just with more resources and a little more room to breathe. I want to understand sleep neurophysiology deeply, both to help people who are struggling with disordered sleep get real diagnoses and real treatments, and to push human performance for operators on the line who are paying a real cost for circadian disruption and poor sleep. My constant fear is not having enough focus to take things all the way to a meaningful next step rather than just publishing papers that do not inform a real path forward. It only makes sense to keep a few irons in the fire, but every single one of them has to be pointed at something that can actually move the field. The glymphatic angle is the piece I am most excited about because it connects sleep to TBI, to neurodegeneration, and to cognition all at once, and I think glymphatic dysfunction will eventually become its own recognized clinical diagnosis with therapies specifically aimed at improving that clearance process during sleep. We also have what may be the largest sleep study in history in the preliminary approval stages right now. It is not public yet, but our lab is going to be a significant part of it, and I am really looking forward to executing on that. For me, that is a fun place to focus and I think it is going to be pretty high yield. That is where I am headed.

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Clinical Corner Authors

Jenova Kempkes is a first-year medical student at the Uniformed Services University of the Health Sciences where she works in the MISL (medical innovations student lab) under the mentorship of Dr. Rodrigo Mateo. Her work focuses on rapid prototyping of novel medical devices that aim to address unmet needs of the military medical community in both austere and clinical settings.

Jason Lee is a first-year medical student at the Uniformed Services University of the Health Sciences with a particular interest in hepatology. Beyond the classroom, he is actively involved in the internal medicine interest group and aims to transition from medical science into a career as a military physician dedicated to advancing patient care.

Srija Seenivasan is an MD-PhD student at the Uniformed Services University of the Health Sciences, where she conducts research in the SWORD Lab under the mentorship of CDR Kent Werner. Her work focuses on the role of microarousals in sleep instability and their relationship to glymphatic function, using computational modeling and polysomnogram data. She aims to develop quantitative microstructure biomarkers of sleep that inform operational readiness.

Trends

The trends section is a collection of work from students and faculty. These pieces are designed to highlight emerging trends in research. Topics include integrating human induced pluripotent stem cells into research, connecting the gut microbiota to health and disease, and how smelling salts may mask concussion symptoms.

From Mouse to Man: How Stem Cells Are Reforming Biomedical Research

Jane Nguyen, Ph.D., Alakesh Bera, Ph.D.

A Turning Point in Translational Research

On April 10, 2025, the U.S. Food and Drug Administration (FDA) announced plans to "phase out animal testing requirements for monoclonal antibodies and other drugs."[1] The National Institutes of Health (NIH) followed with an initiative to expand human-based research and reduce the use of animals.[2] This signaled a notable shift in the biological research landscape for the United States. Recent attention may make the issue seem new, but debates over stem cells versus animal models have persisted since the 1970s, with each offering unique advantages and notable limitations. Animal models have long bridged lab discoveries to therapeutics but the birth of stem cell–based systems and organoids offer promising human-relevant models of tissue architecture and multicellular interactions. Animal models remain relevant in whole-organism contexts as they loop in complex dynamics between organ systems, while stem cells pave the way for more emulative human-based medicines. Each model has distinct strengths, and understanding how their approaches complement one another is key to advancing biomedical research.

The Traditional Gold Standard: Animal Models in Research

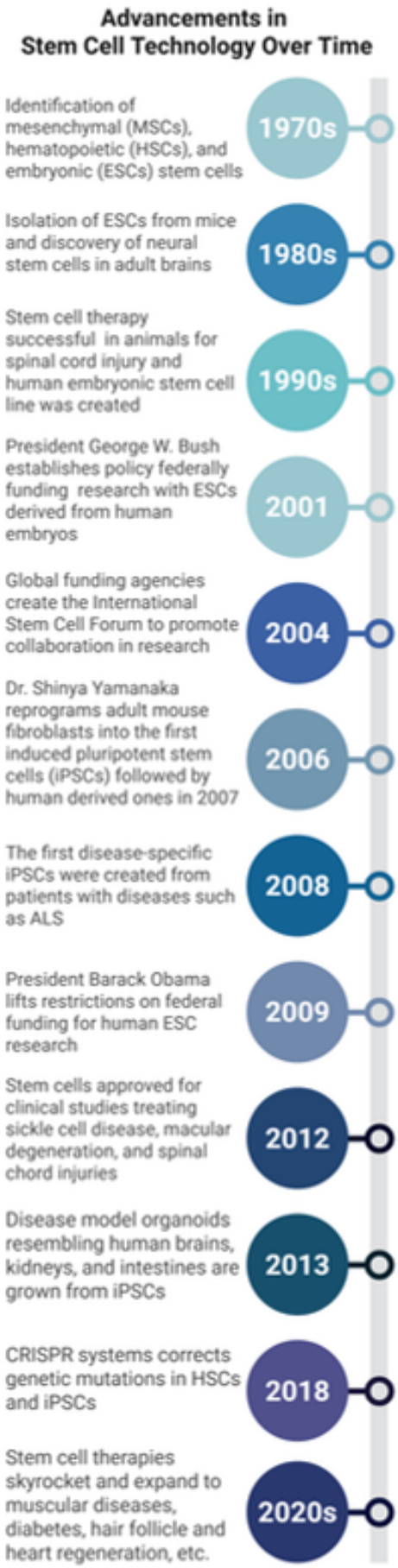
There is strength in studying the whole organism.

For over 2,000 years,[3] animal models, especially mice, have been embedded in the foundation of medical research. Whole-organism approaches capture complex organs, tissues, and immune interplay that isolated cell cultures cannot. Mice are significantly similar to humans, mirroring around 95% of our protein-coding genes.[4] With a short 20-day gestation period, mice rapidly reproduce,[5] providing opportunities for multi-generational studies and efficiently informed predictions of disease impact on humans.

Animal studies hold a long track record of driving major medical advances: polio vaccines,[6] penicillin,[7] tamoxifen to reduce breast cancer,[8-10] and organ transplant techniques.[11-14] Vast and meaningful data from animal models provide key reference points for interpreting new findings. This also means that regulatory agencies like the FDA are deeply familiar with animal-based data, which has traditionally played a central role in drug approvals.

Despite their long-standing use, animal studies do not always translate well to humans. In 2006, biotech company TeGenero tested the monoclonal antibody theralizumab to treat leukemia. Preclinical studies were effective in mice, rabbits, dogs, and monkeys,[15] but catastrophically failed Phase 1 human clinical trials. Fatal inflammatory responses led to the deaths of six out of eight healthy volunteers.[16] It is estimated that only 5% of discoveries from animal studies lead to drugs approved for humans.[17] This low success rate prompts exploration of alternative models.

Another key drawback is that animal models often fail to naturally exhibit complex human diseases, particularly psychiatric disorders. To compensate, animals are often genetically engineered to develop disease-like symptoms. However, these models exhibit extreme versions of the human condition. For example, while humans with Alzheimer's disease may carry a single mutation, mice require multiple mutations to show a measurable disease phenotype.[18,19] This can distort disease biology and limit how well findings apply to patients. Further concerns include the risk of disease transmission, ethical objections to animal welfare, and public discomfort with animal experimentation. Ultimately, these issues have contributed to



increasing interest in human-derived stem cell research.

The Rise of Stem Cell Models:
Milestones That Shaped Modern Stem Cell Research

Stem cells are nonspecific cells originating from embryos, adult tissues, umbilical cords, and placentas. Early research in 1981, isolated the first embryonic stem cells (ESCs) from mice.[20,21] Remarkably, these cells could self-renew indefinitely and differentiate or develop into different cell types. Over the next decades, stem cell research met major discoveries.

In 1997, Dolly the sheep became the first mammal cloned from an adult sheep cell, showing mature cells can generate whole organisms.[22] This led to advances in cellular reprogramming in 1998 when human ESCs were isolated from early-stage human embryos before organ formation.[20, 21, 23-25] Using human embryos ignited ethical and political debate, leading to restrictions on federally funded stem cell research in 2001.[26]

2006 and 2007 saw pivotal breakthroughs when induced pluripotent stem cells (iPSCs) were derived from mouse and then human fibroblasts.[27-30] iPSCs are reprogrammed from adult cells and behave similarly to ESCs but avoid the handling of embryos. iPSCs carry a patient's disease profile, enabling targeted drugs and sparking efforts to produce the first disease-specific cell line for many conditions including amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease.[31]

News of these innovations spread beyond the scientific community and urged the lift of federal funding restrictions on stem cell research in 2009.[32] Since then, research soared, uncovering additional stem cells with unique biology, such as mesenchymal cells (MSCs) and hematopoietic stem cells (HSCs). Around 2010, clinical trials and therapies skyrocketed as industries competed to model human diseases that a mouse could not recapitulate. Stem cell therapies were approved for clinical studies targeting diseases believed to be incurable, irreversible, or terminal, like diabetes and sickle cell anemia. The 2020s saw stem cell–based treatments surge, with applications in tissue regeneration and gene editing-based therapeutics.

A new era of therapeutic innovations dawned with promising advancements in reversing diabetes using regenerative iPSCs to produce insulin-secreting pancreatic cells[33-35] and HSC replacement therapies that alleviated sickle cell disease severity.[36,37] Similarly, iPSC-derived cardiac muscle patches garnered optimism when shown to recover heart function after heart failure.[38,39] In ophthalmology, retinal cells differentiated from human ESCs, iPSCs, and MSCs slowed or reversed vision loss in age-related macular degeneration.[40,41] For nerve damage, human neural stem cell transplants offered hope for improving motor function in spinal cord injuries.[42-45] Subsequently, organoids (3-D stem cell–derived structures mimicking miniature organs) and CRISPR gene editing have enhanced precise modeling and correction of genetic disorders. Disease-specific iPSCs have been genetically altered to ablate pathogenic genes, and then reintroduced into patients to regenerate tissue with corrected, functional cells. These iPSCs were further used to develop organoids that better model multicellular physiology, screen gene-corrected behaviors, and test novel treatments. Combinations of these therapies have been utilized to study genetic disorders like Parkinson's disease[46-52] and cystic fibrosis,[53-56] generating insights often missed in animal models. This allows patient-specific study of diseases and the creation of personalized therapies addressing root causes, not just symptoms.

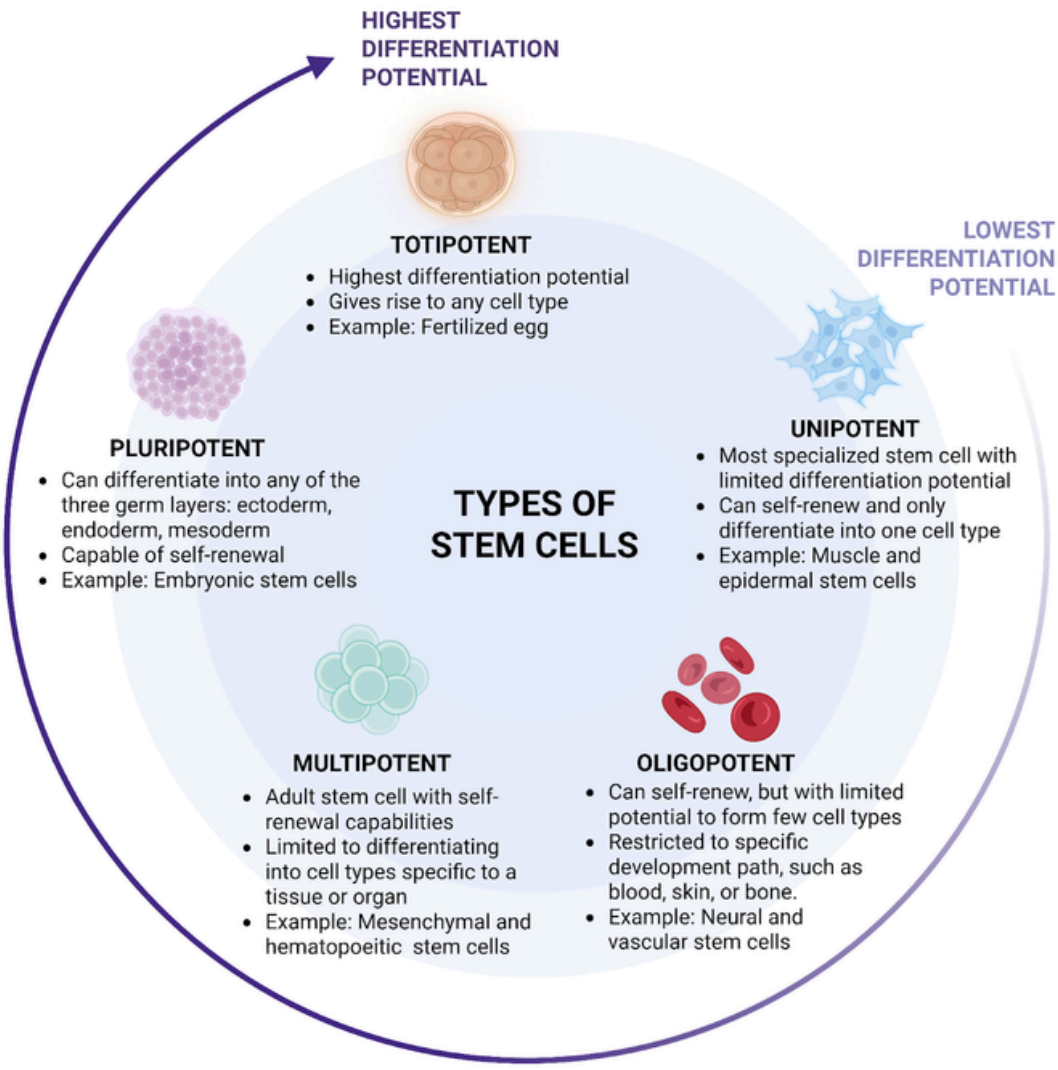
The Spectrum of Stem Cells: From Potential to Practice

To understand how these innovations are possible, we turn to the underlying stem cell biology behind them. There are five distinct types of stem cells that delineate differentiation potential, providing personalized ways to model tissue-specific conditions. Totipotent stem cells, like fertilized eggs, have the highest differentiation potential and can build a whole being from scratch. In contrast, pluripotent stem cells only produce the being's organs across the three germ layers:[25,57,58] mesoderm (heart, kidneys, skeletal muscles), ectoderm (nervous system, skin), and endoderm (lungs, liver, stomach).

Unlike pluripotent stem cells, multipotent ones are limited to becoming cell types within their tissue of origin. For example, MSCs from bone marrow are restricted to differentiating into bone (osteocytes) or cartilage (chondrocytes). Oligopotent stem cells have a narrower potential, producing only a few related cell types, such as neural stem cells giving rise to neurons or glial cells. Lastly, unipotent stem cells are the most restricted, capable of producing only a single cell type - like keratinocytes from epidermal skin cells.[57,59,60]

Relative to animal models, human stem cells are a sustainable and renewable resource. They can be rapidly grown in days, maintained in culture long-term, and cryopreserved for future use. As accessibility improves through shared national initiatives, such as well-characterized iPSC repositories, stem cell research is becoming more attainable for a broader range of laboratories.

Despite their promise, stem cell models face challenges. From a modeling perspective, stem cells still fall short in fully replicating the immune, hormonal, and multi-system functions of a whole organism. Emulating aging, for example, is difficult – what does it mean for a stem cell to be "old," and how accurately can age-related diseases be reproduced? Cost and technical expertise also pose barriers, as do the high costs of resource-intensive animal research.

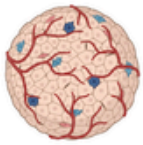


Stem cells require nutrients and stringent routine care. Maintaining stem cells entails feeding them (or changing culture media) daily. One bottle of media can reach up to $500, meanwhile a bottle of media for immortalized or primary cells range around $50 (with media changes recommended every 2–3 days). Ongoing advances in co-culture systems, organ-on-a-chip platforms, and multi-organoid integration aim to address these limitations, but these technologies are still under development.

Ethical concerns circle around gene editing and cloning, begging the question: Where should we draw the line on manipulating human cells?

CRISPR editing technologies can cause off-target effects, including gene disruption (raising cancer risk), base-editing errors resulting in unwanted mutations, and transgenic integration, or accidental insertion of engineered DNA into the host genome.[61,62] If unchecked, these errors propagate, leading to long-term impacts on future generations of disease modeling and therapeutics. Altering human genetics is controversial, with ongoing debate over morals and safeguards. Regulatory frameworks for evaluating stem cell-based data are multi-pronged and evolving, complicating their adoption in drug development pipelines.

	ANIMAL MODELS	VERSUS	STEM CELL MODELS
PROS	Whole-organism dynamics		Patient-specific modeling and personalized medicines
	Long-standing use yields decades of historical data and regulatory familiarity		Avoids ethical concerns with animal research
	Rapid reproduction in models like mice enable longitudinal studies and generational research		Advanced organoid systems can mimic human-specific tissue architecture and organ crosstalk
CONS	Low predictability for human translation (~5% of findings lead to approved drugs)		Cannot fully replicate whole-organism complexity (immune and hormonal responses)
	Animals do not naturally develop many human diseases and genetic modifications can distort disease biology		Regulatory frameworks and validation pipelines are still evolving
	Ethical concerns and public discomfort with animal experimentation		Ethical concerns remain with gene editing and cloning technologies
	Resource-intensive and expensive (e.g., specialized facilities, food, veterinary care)		Limited long-term historical data
			High cost and maintenance (e.g., expensive culture media, daily feeding)



Choosing the Right Model: Basic Discovery vs. Therapeutic Translation

One size does not fit all. The choice between animal models and stem cell-based systems often depends on the research question. Animal models may be better suited for studying systemic effects, drug toxicity, and whole-body immune responses. In contrast, stem cell models may excel at uncovering human-specific disease mechanisms, testing patient-specific therapies, and modeling early disease processes.

For basic science, stem cells offer powerful tools to study cellular development and genetic regulation. For translational and therapeutic research, a combination of models may provide the most reliable path forward. It is important to match the model to the question.

Toward a More Integrated Research Future: Complement, Not Competition

The transition from animal models to stem cell–based research is neither simple nor immediate. Stem cell approaches must be rigorously tested and validated, often using existing animal data as a reference point. However, if animal models poorly reflect the human condition in certain diseases, their role as the gold standard for validation should be reconsidered.

Moving forward, close communication between scientists and regulatory bodies, such as Institutional Review Boards (IRBs) and Institutional Animal Care and Use Committees (IACUCs), will be essential in determining which model is most appropriate for each study. Rather than viewing stem cells and animal models as competitors, they should be seen as complementary

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Moving forward, close communication between scientists and regulatory bodies, such as Institutional Review Boards (IRBs) and Institutional Animal Care and Use Committees (IACUCs), will be essential in determining which model is most appropriate for each study. Rather than viewing stem cells and animal models as competitors, they should be seen as complementary tools. Based on current evidence, there is no justification for the complete abandonment of either approach. Instead, leveraging the strengths of both systems offers the most promising strategy for advancing biomedical research and improving human health.

About the authors

Dr. Jane Nguyen is a Postdoctoral Fellow advised by Dr. Alakesh Bera in the Department of Anesthesiology. Her current research focuses on developing induced pluripotent stem cell (iPSC)-derived skeletal muscle organoids to study rare muscular diseases including malignant hyperthermia and Duchenne muscular dystrophy. Previously, her stem cell experience reaches back to Johns Hopkins University where she developed iPSC-derived vascular models to study the effects of hypoxia and cigarette smoke on the brain and recently received her Ph.D. in Chemical and Biomolecular Engineering.

Dr. Alakesh Bera is an Assistant Professor in the Department of Anesthesiology and Director of the Malignant Hyperthermia Testing Core Laboratory. His research group specializes in muscular dystrophy and related pathologies. The lab's current work uses stem cell-derived musculoskeletal models to study malignant hyperthermia, exertional heat illness, and Duchenne muscular dystrophy, aiming to advance therapeutic understanding of these critical conditions.

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By Zamantha Manalansan-Roberson & David Burmeister, PhD

You Are What You Eat: *The Digestion to Disease Pipeline*

Gut Microbiome

The human body hosts a complex microbiome of bacteria, viruses, and fungi. Dominated by Bacteroidetes, Firmicutes, Actinobacteria, and Proteobacteria, these microbes collectively support digestion, immunity, and metabolic homeostasis.[1,2,8,9] Each person's microbiome is unique and shaped by genetics, diet, and environment.[11,12] Each plays an important role in gut function, supporting digestion, immune function, and gut balance through carbohydrate breakdown, short-chain fatty acid (SCFA) production, immune training, and maintenance of favorable conditions for beneficial microbes (Fig. 1).[2] Together, they help maintain balance in digestion, immunity, and inflammation.

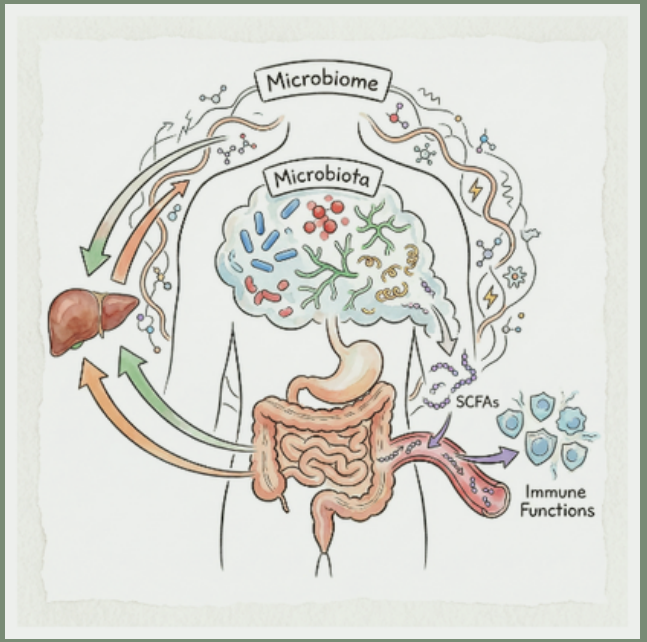

Figure 1. Illustration of the relationship between the gut microbiome (the community of microorganisms) and microbiota (the organisms themselves), and how they interact with the body. Microbes in the gut produce metabolites such as short-chain fatty acids (SCFAs), which enter circulation and influence immune function and organ systems. The diagram highlights bidirectional communication between the gut and organs such as the liver, as well as systemic signaling pathways that connect microbial activity to inflammation, metabolism, and overall physiological balance.

Changes in the gut microbiome also vary along the digestive tract and between individuals, and disruptions have been linked to diseases such as Crohn's disease, non-alcoholic fatty liver disease (NAFLD), Parkinson's, and chronic obstructive pulmonary disease (COPD).[45-48] These conditions share common features of chronic inflammation and immune dysfunction, suggesting the microbiome plays a role in regulating systemic health beyond the gut.

Microbiome Development

The gut microbiome develops across each stage of life, from well before birth to adulthood. For example, prior to

birth, microbiota can colonize a once-sterile fetal gastrointestinal (GI) tract via maternal bloodstream migration or direct exposure to the placenta or amniotic fluid.[5-7] Though bacterial transmission routes vary, the three common factors that influence colonization of the infant intestinal microbiome are gestational age, mode of delivery, and antibiotic therapy.[8-10]

At three years old, a child's microbiome resembles the bacterial diversity and structural complexity that closely mirrors that of an adult.[11] This developmental milestone is characterized by a shift toward a stable bacterial community, dominated by a high abundance of both *Firmicutes* and *Bacteroidetes* phyla.[11,12] As development continues into adolescence, systemic factors such as pubertal hormonal shifts, dietary changes, and psychological stress exert significant influence on both immune maturation and neurobiological function.[13] These physiological and environmental drivers represent two underlying processes that concurrently reshape the gut microbiota. Consequently, these shifts in composition and functional diversity during adolescence contribute to the long-term trajectory of the microbiome across the human lifespan.

In adulthood, beneficial gut bacteria, such as Bifidobacterium, are typically abundant and help maintain gut health by preventing the overgrowth of harmful microbes.[24] However, as people age, changes in the microbiome occur due to factors such as a weakening immune system and increased medication use.[25-27] These changes often include a decline in "core" beneficial bacteria, including Bifidobacterium and those that produce butyrate, a compound that supports the gut lining.[25,26] As these protective microbes decrease, the gut barrier can weaken, allowing bacterial products to enter the bloodstream and trigger chronic, low-grade inflammation, often referred to as "inflammaging."[27] At the same time,

A balanced microbial community supports immune function, maintains the gut barrier, and promotes overall resilience.

potentially harmful bacteria may increase, shifting the gut toward a more inflammatory state. Together, these changes can disrupt overall health and may contribute to the development of age-related diseases. A balanced microbial community supports immune function, maintains the gut barrier, and promotes overall resilience, while disruptions such as illness or antibiotic use can reduce diversity and increase the risk of dysbiosis.[48]

As these changes accumulate, their effects extend beyond the gut. Age-related microbial imbalances have been linked to diseases in other organs, including NAFLD, where microbial metabolites influence liver fat accumulation and inflammation.[46] Similarly, through the gut–lung axis, a depleted microbiome may worsen chronic respiratory conditions, such as COPD, although this may be improved with interventions like prebiotic fiber.[45] These findings suggest that breakdowns in gut–microbe balance can contribute to multi-organ dysfunction, ranging from inflammatory bowel conditions like Crohn's disease to metabolic and respiratory disorders.[47,48] Understanding these connections provides a foundation for developing targeted therapies to support health across the lifespan.[47]

Gut Dysbiosis

While the GI tract facilitates nutrient absorption, commensal microbiota functions as a critical

immune–metabolic interface that regulates systemic health.[15] These microbes perform essential metabolic tasks, such as synthesizing vitamins and fermenting indigestible fibers into SCFAs that regulate host energy balance and weight.[16,28] Lifestyle factors like sleep and stress influence gut motility and microbial balance (Fig. 1).[15] Physical activity is a major driver for this system; for example, a study of professional rugby players utilized fecal samples and blood inflammatory markers to demonstrate that high-intensity exercise, and high protein intake, significantly increased the abundance of the *Firmicutes* phylum.[29] This shift is biologically significant because these bacteria are primary producers of butyrate, which reinforces the intestinal barrier. This barrier consists of a physical mucus layer and "tight junction" proteins that maintain selective permeability, preventing the migration of inflammatory toxins into the bloodstream.[15,29] Without this structural integrity, the gut undergoes a shift toward dysbiosis, where beneficial commensals are outcompeted by opportunistic microbes that trigger systemic inflammation (Fig. 2).[15,28]

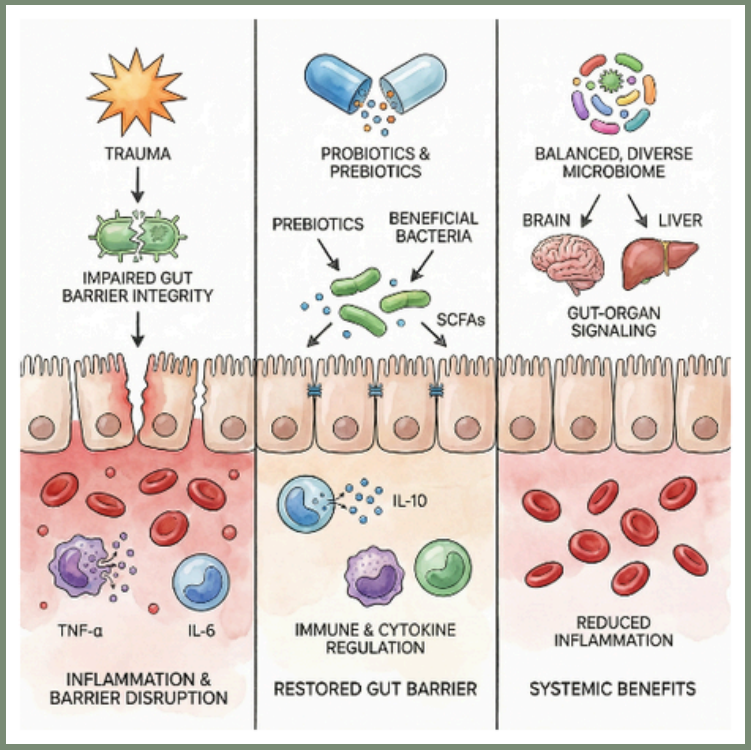

Figure 2. Contrasts three states of gut health: disruption, intervention, and recovery. On the left, trauma damages the intestinal barrier, allowing inflammatory molecules (e.g., TNF-α, IL-6) to enter circulation and promote systemic inflammation. The center panel shows how probiotics and prebiotics support beneficial bacteria and SCFA production, helping regulate immune responses (e.g., IL-10) and restore barrier integrity. The right panel depicts a balanced microbiome, where reduced inflammation and effective gut-organ signaling (e.g., brain and liver communication) contribute to improved systemic health.

Military Relevance

Trauma

The gut microbiome communicates with other organs via gut-organ axes, influencing systemic health (Fig. 1).[45-48] The intestine has been called the “motor” of critical illness by driving inflammation and triggering multiple organ dysfunction (MOD) through this complex crosstalk.[31] Trauma is a major disruptor, triggering widespread systemic complications through gut-organ crosstalk. Trauma can compromise the intestinal epithelial barrier, reduce gut perfusion, and create gut dysbiosis and systemic inflammation (Fig. 2).[18,19] Severe injury rapidly alters the gut microbiome, correlating with worse outcomes.[14,19]

Severe trauma disrupts the gut microbiome, and clinical interventions such as high-volume blood transfusions have been associated with microbial diversity profiles that more closely resemble those of healthy individuals compared to non-transfused patients.[18] This effect is thought to arise from improved perfusion which helps maintain oxygen gradients in the intestinal mucosa that support anaerobic, commensal microbial niches. By stabilizing these microenvironments, transfusion therapy may help preserve key microbial populations during acute physiological stress.

The extent of dysbiosis is further exacerbated in

Trauma is a major disruptor, triggering widespread systemic complications through gut-organ crosstalk.

polytrauma scenarios, where combined injury types (e.g., radiation plus burn or mechanical injury) produce synergistically worse outcomes, including increased mortality and accelerated tissue "pathobiome" degradation.[32,44] In this context, the gut "pathobiome" shift correlates with host tissue injury severity. Importantly, biodosimetric studies suggest that microbial diversity loss may serve as an early biomarker of radiation-induced intestinal and hematopoietic damage.[43] Collectively, these findings support the gut microbiome as both a dynamic indicator of injury severity and a potential therapeutic target.

Radiation and Burn Injuries

There are cases of microbiome alterations following polytrauma, or combined injuries (CI) which occur commonly in severe attacks using nuclear or radiologic weapons. Studies examining radiation combined with skin burns have shown greater immune dysregulation, increased inflammatory signaling, and higher susceptibility to systemic bacterial infection than radiation exposure alone.[43,44] This intensified inflammatory response is partly driven by elevated levels of inflammatory molecules, such as interleukin-6 (IL-6) and C-reactive protein (CRP).[44]

These systemic effects also significantly disrupt the gut microbiome and intestinal barrier. Recent work using a large-animal porcine model of radiation and burn injury demonstrated that animals exposed to CI experienced weight loss, diarrhea, and reduced appetite, accompanied by increased intestinal cell death, elevated interleukin-1β (IL-1β), and declining gut lining health. Microbiome sequencing further revealed changes in bacterial families associated with intestinal dysfunction and liver injury, supporting the idea that CI further disrupts the gut-liver axis.[17]

Studies examining burn injuries have reported increases in opportunistic pathogens within the gut microbial community,[35] while radiation exposure has similarly been linked to the expansion of microbes associated with inflammatory responses.[36-42] Overall, these findings suggest that CI can amplify stress on the body. This leads to increased inflammation, immune suppression, and organ damage, which ultimately contributes to higher mortality rates compared to single-injury exposure.[32,43,44]

Therapeutics

Given the systemic implications of the microbiome across development and trauma, therapeutic strategies must shift toward restoring gut microbial homeostasis through both accessible and field-deployable interventions. Studies show that restoring or modulating gut bacteria can reduce inflammation and support the intestinal barrier in conditions like immune-related colitis and radiation-induced gut damage (Fig. 2).[20,22] Probiotics have also been shown to help preserve intestinal structure in experimental models[23] and may protect against harmful bacterial overgrowth.[24]

These modern interventions utilize a "therapeutic symphony" of probiotics, prebiotics, and postbiotics to address specific microbial deficits.[33] Probiotics provide live bacteria, prebiotics nourish them, and postbiotics deliver functional metabolites (Fig. 2).[33] These bioactive byproducts,

such as SCFAs, provide immediate metabolic benefits without requiring the stability of live cultures, making them ideal for high-stress environments where refrigeration is unavailable.[33]

These interventions also support neurological resilience via the gut-brain axis.[34] By modulating the vagus nerve and producing neurochemicals like serotonin precursors, a balanced microbiome stabilizes the host's circadian rhythms and sleep architecture.[34] This is critical for recovery; restorative sleep prevents the sympathetic nervous system stress that further compromises gut integrity. By leveraging these tailored biotics and advanced interventions like Fecal Microbiota Transplantation (FMT), researchers are transforming the gut into a primary lever for both physical survival and neurological recovery in the most challenging clinical environments.[33,34]

Current Research and Future Directions

Building on these mechanism-driven therapeutics, current research focuses on how specific microbial functions support recovery after injury. Advances in next-generation sequencing, a genetic technique that identifies bacteria based on unique DNA segments, allow scientists to map the gut microbiome with high precision. Grouping bacteria by taxa links microbes to barrier repair, inflammation, and immune regulation.

Additionally, certain taxa produce SCFAs, which help maintain the intestinal lining and regulate immune responses, while others influence pathways involved in systemic inflammation. Connecting these functions to microbial composition supports the development of targeted therapies, including probiotics that restore beneficial bacteria and postbiotics that deliver key metabolic products.

Gaps remain in optimizing therapies for trauma and accounting for individual microbiome variation. Ongoing research continues to explore how gut microbes influence recovery across organ systems, particularly through gut-brain and gut-immune signaling. Overall, the gut microbiome regulates systemic health and may guide precise therapies in clinical and field settings.

About the authors

Zamantha Manalansan-Roberson is a 2nd-year MCB PhD student in the Department of Medicine, mentored by Dr. David Burmeister. She studies how chronic intestinal injury affects the gut microbiome and inflammation, and how these changes contribute to systemic disease.

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Re-Energizing or Re-Injuring? Why Smelling Salts Could Mask Concussion Symptoms

Alexandra Graninger & Zach Wilson, SIDC

Few things could bring a 300-pound lineman or a star quarterback to tears as quickly as a whiff of smelling salts. Also known as ammonia inhalants (AI), smelling salts have been used for decades by athletes to get a quick jolt of energy during games. In 2025, the National Football League (NFL) officially drew a line in the sand by banning their use during pregame activities, games, and halftime, including on the sidelines and in the locker rooms.[1]

Behind the Ban & Player Pushback

The AI ban in the NFL was recommended by the NFL's Head, Neck, and Spine Committee. The committee includes both NFL-affiliated and independent medical professionals from Johns Hopkins, West Virginia University, and Stanford Medical Center, as well as physicians who run independent practices, to provide relevant input on player safety.[2]

The basis for their recommendation leans heavily on a 2024 warning from the Food and Drug Administration (FDA) that commercial AIs lack sufficient evidence supporting their safety or efficacy.[1,3] The FDA warns consumers against purchasing specific brands of inhalants marketed to promote alertness and boost energy due to their unsubstantiated claims of benefit, unregulated nature and potential for adverse events.[3]

Admittedly, this didn't go over very smoothly with the players. One of the most outspoken examples is San Francisco 49ers player George Kittle. After receiving news of the ban, the tight end described himself as distraught, considering retirement after a nine-year career; he expressed hope that a middle ground could be found on authorizing the use of AIs.[10] Beyond Kittle and the NFL, many professional athletes would say AIs help them focus in chaotic crowds or are part of a pregame routine (not a superstition).

The players' perspective is important not only because it's their health that others are arguing over at the end of the day, but also because of the relationship between the players and the game itself. Instituting rules that alter players' pregame ritual, and therefore players' mindset entering play, could lead to consequences on the field. Put

simply, you're just not in the zone if someone else's rules are disrupting your flow.

To those of us who are lab rats, these might seem like loose excuses. So what if it breaks your ritual? Is that really doing anything for you anyway? But imagine if your supervisor said that you can't have that extra cup of coffee or espresso shot to help get you through a data analysis slump on a tight deadline. Ditching the coffee wouldn't ruin your life, but it would be an annoying hindrance. This might come across as telling you what to do unnecessarily rather than as guidance grounded in solid evidence, since you have done it without harm for years.

After players expressed their concerns, an important stipulation to the ban was later noted by the League. It was clarified that players can bring their own smelling salts, but the NFL cannot provide them.[11] This raises an interesting question: whether the NFL is really worried about player safety or is attempting to avoid a potential legal situation.

The ban could come as a delayed response to a court filing where several former Chiefs players attempted to sue the team. They claimed that, among other reasons, the NFL provided them with AIs in order to mask concussion symptoms to keep them out on the field.[12] More recently, in 2024, Bills quarterback Josh Allen came under fire when a Bills staff member was seen handing him a smelling salt prior to entering the NFL's blue medical tent for a head injury evaluation after a tough hit. Allen passed his evaluation, leading to speculation of a cover up.[13]

Among other reasons, situations like this helped motivate the NFL to award over $35 million in brain and concussion-related research.[19] These examples highlight the importance of ensuring that treatments and supplements used within an organization are aligned with expert recommendations to limit harm, but also that the players' opinions can't be ignored. Perhaps a better solution is to allow players to have smelling salts, regardless of who provides them, but they just can't be used immediately before entering concussion protocol. Trainers, sideline staff, and even independent concussion experts (who make the decision to pull players for concussion protocol) can all keep eyes out to prevent smelling salts from being used before players undergo in-game concussion testing. In addition, players can be informed of the risks of returning to the field with an undiagnosed concussion to try to prevent AIs from being sneaked to players before concussion assessments.

Biology & Effects of Ammonia Inhalants

Despite the widespread use, it's still somewhat unclear how ammonia inhalants work biologically. Ammonia is a pungent, colorless gas that occurs naturally in both the environment and living organisms.[14] Smelling salts typically contain around 15% ammonia mixed with water, other solvents, and/or other perfumes.[14] Once the ammonia gas is absorbed by the moisture in the mucus membranes of the nose and lungs, it forms ammonia hydroxide.[4] Evidence suggests that when someone inhales ammonia vapors, this irritates the airway mucus membranes. Chemoreceptors, small molecules designed to detect chemicals present in your airways, detect ammonia and alert the trigeminal cranial nerve (Figure 1). This sends reflexive, sympathetic nervous system signals to the medulla, which is part of the brainstem.

This results in elevated vital signs and increased mucus secretions, such as increased heart rate and a runny nose, in response to the irritant.[5] It has also been reported that ammonia inhalants

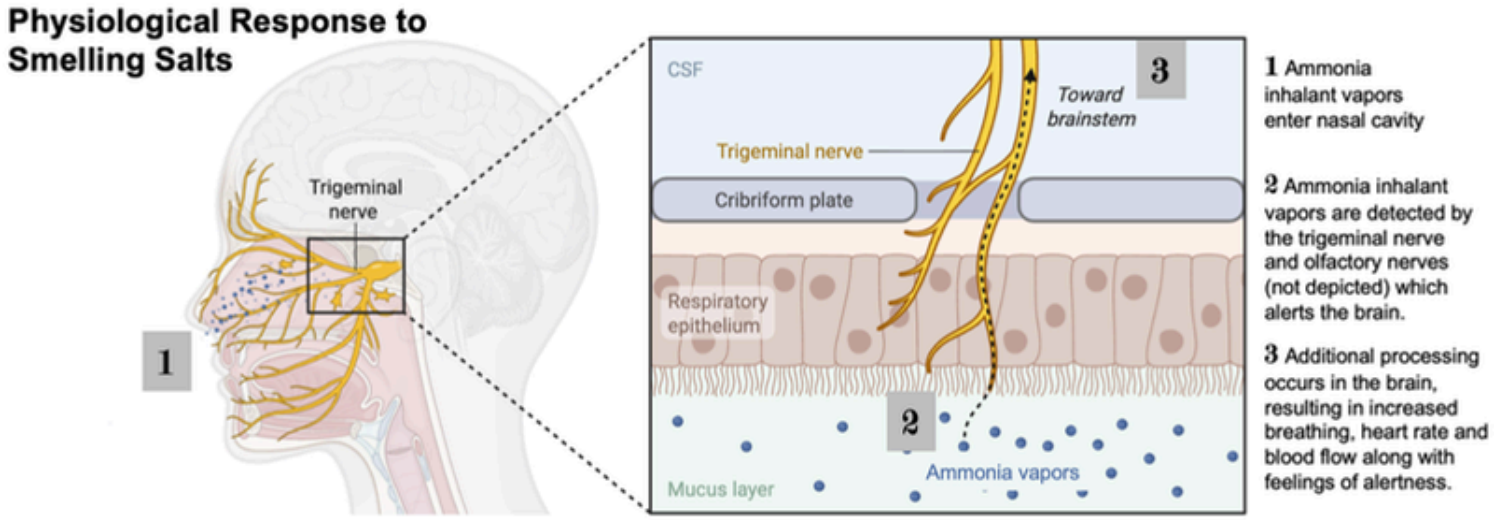

Figure 1. Physiological response to ammonia inhalants. Figure created with BioRender.

can increase blood flow in the middle cerebral artery,[5,6] one of the main arteries supplying important brain regions such as motor areas and parts of the temporal and frontal lobes. Due to the effects of ammonia vapors on blood flow, they've been used as a relatively outdated and slightly unnecessary treatment for fainting. Fainting is often due to blood vessel constriction; therefore, the vasodilation caused by ammonia helps wake individuals who have fainted.[6] However, this treatment is questionable because typically people will wake up from fainting even without ammonia inhalants.

	Concentration (ppm)
Noticeable odor but no health effects	5 - 20
Minimal irritation	5
Moderate irritation	9 - 50
Ammonia in Smelling Salts	50 - 100
Definite irritation	125 - 137
Maximum short exposure tolerance	300 - 500 (for 30 - 60 minutes)
Coughing, vomiting, pulmonary edema, chest pain, shortness of breath, possible death	1,500 - 10,000

Table 1. Amount of ammonia and related effects. Modified from (16), (17) and (18).

For context, athletes generally only wave smelling salts (50 - 100 parts per million [ppm] of ammonia)[15] around their face for a few seconds, though this exposure can be repeated throughout the game. According to The National Institute for Occupational Safety and Health (NIOSH), ammonia levels do not become dangerous until they reach 300 ppm and are inhaled for 30 minutes[16] (Table 1). So in other words, athletes are exposed to ⅙ -⅓ the levels considered dangerous for a few seconds, say even a few minutes, estimating high for repeated exposure throughout the game.

Anecdotally, athletes often swear by ammonia inhalants helping them stay alert and focused during a game. Despite minimal to no actual performance benefits during exercise by any observable biological mechanism, AIs do seem to provide psychological energy and wakefulness.[6] It is this sudden alertness from ammonia inhalants that can distract from diagnosing proper head injuries and studies have recommended against using AIs after concussions.[6,9]

A Microcosm of a Bigger Issue

Regardless of whether the AI ban is due to potential legal troubles or a true concern for players, there is a bigger problem at hand. The larger point of banning AIs is to reduce concussion risk in sports, and even more broadly,

reduce general risk of any sports-related injury. Much work is still being done to minimize this critical risk. However, there's a safe way to maintain the integrity of the game. The players' safety needs to be protected, but any steps taken to increase safety need to be based on concrete evidence. While safety is a main concern in sports, unfortunately, to some degree, it's an occupational hazard that will never be completely eliminated even with extensive safety precautions. Just like healthcare workers can be exposed to hepatitis and construction workers can be exposed to injuries from heavy machinery, athletes can be exposed to head injuries.

Sports are something that have brought Americans – athletes and scientists alike – together for generations. Understanding these perspectives, which sometimes drastically oppose each other, is the only way to move the game forward competitively and safely for everyone's benefit.

About the Authors

Alex Graninger is a fifth year Neuroscience PhD student, graduating this summer. She works in Dr Prasanna Krishnan's lab studying intracellular protein trafficking and lysosomal function related to Alzheimer's disease in human cells.

Zach Wilson is an Assistant Professor in the College of Allied Health Sciences Education & Training Administration & Leadership and Surface Independent Duty Corpsman programs of instruction. He studies the development and execution of processes to maximize the learning outcomes for health professions students.

AI statement: No ammonia inhalants or artificial intelligence were used while writing this article.

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Conferences

Our broader USU community has reviewed recent conferences they've attended in this section. Attendees provide their first-hand experience of these conferences.

INTERNATIONAL MEETING ON SIMULATION IN HEALTHCARE

MAJ JULIA CATANESE
Nursing PhD, Graduated Spring 2026

San Antonio, TX
January 10-14, 2026

The International Meeting on Simulation in Healthcare (IMSH) was held in San Antonio, Texas, this year. IMSH is the largest international conference dedicated to healthcare simulation, education, and assessment, bringing together more than 4,500 clinicians, educators, researchers, and industry leaders over four days each January. The conference featured plenary speakers, over 800 educational sessions and workshops focused on translating and communicating research findings, hands-on learning labs, and an exhibition hall showcasing the latest simulation technologies. I am grateful to the Daniel K. Inouye Graduate School of Nursing for sponsoring my attendance. I presented a poster summarizing findings from a systematic review completed as part of my coursework. In addition, I attended several federal meetings where military and Department of Veterans Affairs IMSH attendees convened to report program activities, network, and generate collaborations across the Military Health System and the VA.

One particularly impactful session, led by Dr. Mary Sturgeon and colleagues, focused on joint operational readiness training for active-duty and reserve medical teams, highlighting how simulation supports readiness across diverse operational environments, including maritime and austere settings. Across IMSH, there continued to be a strong emphasis on competency-based education, rigorous assessment of learner performance, and the growing use of artificial intelligence to support performance assessment, feedback, and simulation scenario design. A particularly engaging plenary session, “Creative Trespassing,” delivered by Tania Katan, reinforced how innovation often emerges from constraints, an idea that resonated in many discussions on solutions for readiness-focused and resource-limited military environments.

Conference proceedings and abstracts are forthcoming and will be published in a summer issue of Simulation in Healthcare: The Journal of the Society for Simulation in Healthcare. For those interested in simulation or healthcare education research, IMSH will be held next year, January 23–27, 2027, in New Orleans, Louisiana.

THE INTERNATIONAL SOCIETY FOR TRAUMATIC STRESS STUDIES Annual Meeting

Baltimore, MD
September 17-20, 2025

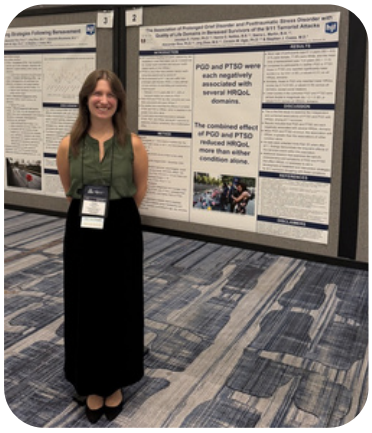
HANNA NETTLES
CENTER FOR THE STUDY OF TRAUMATIC STRESS

Braving the seasonal influx of lanternflies, I attended the International Society for Traumatic Stress Studies (ISTSS) 41st Annual Meeting last fall in Baltimore, Maryland. I participated in the conference as part of the Center for the Study of Traumatic Stress (CSTS) within the USU Department of Psychiatry. The meeting theme, "Frontiers in Traumatic Stress: Global Perspectives and Creative Solutions," was reflected in the wide range of flash talks, panels, and presentations exploring innovative approaches to trauma research and treatment.

I was grateful for the opportunity to present alongside a small group of scientists and study coordinators from CSTS. It was especially rewarding to see the progression of our project – from the time I joined the study team during data collection to the presentation of our first analyses. During the poster session, I answered questions and engaged in discussions that expanded my understanding of potential future directions for the project and related research areas. One memorable interaction occurred when an attendee introduced himself after our conversation; we realized we had previously corresponded by email while I was assisting CSTS scientists as an editorial assistant for a Special Issue. It was great to have the chance to speak in person and connect beyond our computer screens.

One standout session for me was "Inner Resources Mindfulness Techniques for Distress Reduction & Emotion Regulation in Trauma Treatment." The presentation explored how mindfulness strategies can be tailored to individual patient needs. While mindfulness was introduced broadly, the use of patient vignettes demonstrated how techniques can vary in structure and in the degree to which they encourage distraction from or engagement with traumatic experiences during meditation and therapy.

With such a diverse range of sessions offered throughout the conference, it was easy to fill each day from sunrise to sunset with presentations. Preparing in advance by ranking the presentations I was most interested in helped me build a schedule that made the most of the three-day meeting. The sheer number of events was overwhelming in the best way possible. Speakers were both knowledgeable and enthusiastic, and the conference created a welcoming environment for discussing shared interest in trauma research and discovering unexpected connections between projects.



INTERNATIONAL BIONIC LIMB RECONSTRUCTION SYMPOSIUM

2LT ZACHARY BAILEY
MEDICAL STUDENT

Vienna, Austria
December 3-5, 2025

The International Bionic Limb Reconstruction Symposium focused on advanced limb salvage and amputation techniques to maximize functional outcomes in patients. There were about 500 participants from across the world, significant numbers from the US, UK, Germany, Austria, and Italy. The program consisted of research talks from leading academic professors and surgeons, interleaved with live feed from a surgical operating room where the amputation techniques discussed were being put into practice. Additionally, there were two days of cadaver surgical training from the attendings who have been pioneering these techniques, including a transfemoral demonstration from Dr. Rickard Branemark and his Integrum osseointegrated implant.

This field continues to be pushed forward by bionic visionaries like Dr. Hugh Herr, who gave a talk on his latest work providing intuitive, biomimetic sensory feedback in lower limb amputees during ambulation. There is still much room to advance in the realm of implantable interfaces for high-resolution motor control and sensory feedback, but surgical leaders like Dr. Oskar Aszmann and Dr. Paul Cederna demonstrated their work to integrate implantable devices and these distinct surgical techniques in staged procedures to re-enable patients after severe functional loss.

For my benefit, this was the ideal audience to present my PhD work on improving spatially selective stimulation in peripheral nerve interfacing, as my work centered on surgically-informed electrode array device design. It's always a bit intimidating showing your work to the experts in the field, but it led to fruitful conversations during the conference and clinic collaborations that could take my work to the next phase. But we all know you can't go to an academic conference without a little bit of cultural expansion, sightseeing, and fun. So, alongside members of my previous lab at Imperial College London and new colleagues here at USUHS, I saw how the Viennese royalty lived at Hofburg Palace and Schönbrunn Palace, learned how medicine progressed through the ages in the National Library, and practiced the local Austrian imbibition technique!

While it was fun and a great academic experience, we were also reminded why we were all there, doing the research we do. Patients with amputations were present and discussing their injuries and subsequent reconstructive surgery, detailing the challenges they still faced, hoping to provide insight into how we keep patient-focused care as the priority.

American Academy of Pediatrics National Conference and Exhibition

Denver, CO
September 26-30, 2025

MAJ KATHERINE JONES, MD
SOM FACULTY

The American Academy of Pediatrics National Conference is a robust meeting of over 10,000 pediatricians and other clinicians. From a military perspective, it is a hugely important conference for uniformed pediatricians. It is the site of the AAP Section on Uniformed Services annual meeting, where we discuss major topics affecting the health of children of service members. This allows us to stay up to date on the latest topics in pediatric medicine and provides us a time and place for morale building with our fellow pediatricians.

The author and two colleagues. Maj Jones is on the right.

I was fortunate to attend this meeting in Denver in September 2025, and I gained a lot of insight into the impact of environmental exposures on the health of service members and dependents from leading experts in environmental science and sustainability. I also learned about how sustainability practices within the Defense Health Agency can help us to ensure we have sufficient equipment to optimally care for our patients while still working within budgetary constraints. I also attended talks about the impact of phones/digital devices in schools and the wide variety of current policies in place at school districts around the country.

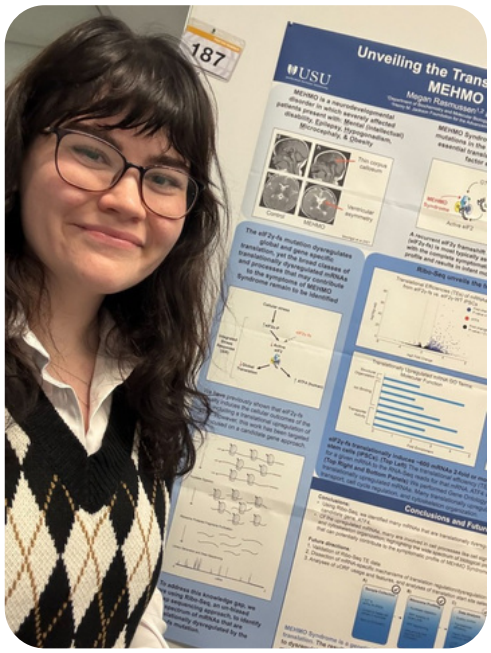
As a pediatric nephrologist, I was thrilled to have the opportunity to hear about the latest innovations in the care of children and adolescents with kidney stones – both a personal interest and operationally-relevant topic. One practice change I have made as a result is to more strongly consider use of alpha antagonists in the setting of acute urolithiasis, which is something I had previously counseled against. During the Section on Uniformed Services meeting, I was able to present work by our Pediatrics Education Division to leverage large language models in the evaluation of written history and physicals- and our team took home first place in our category!

Another highlight of the meeting for me was getting to meet with another uniformed pediatric nephrologist - there are only 3 of us in the Army right now. We often talk on the phone and e-mail about cases and practice challenges, but meeting face to face provided space and time to discuss issues facing both our patients and our specialty.

European Molecular Biology Laboratory Conference

MEGAN RASMUSSEN
MCB PHD STUDENT

Heidelberg, Germany
September 3-7, 2025



Attending the 2025 EMBL Conference on Protein Synthesis and Translational Control in Heidelberg, Germany, was a profound experience that perfectly bridged the history of molecular biology with the art of its future. As an in-person attendee, I found the atmosphere at the EMBL Advanced Training Centre (ATC) electric. The crowd was massive, at least 400 enthusiastic scientists, creating a lively environment dedicated entirely to discussing the mystery of translation and protein synthesis. The architecture of the ATC itself served as a constant reminder of the beauty of science, with its famous double-helix ramps designed like our DNA. Walking up the ramps to move through the poster sessions felt like a journey through the biology we study. The posters were placed throughout the entirety of the helix ramps, ensuring a natural flow of collaboration and communication where every presenter was visible to the energetic crowd.

Scientifically, the conference highlighted the direction of the translation field. It was clear through the oral and poster presentations that the future of studying ribosome biogenesis and protein assembly lies in high-resolution structural biology. Many talks focused on how cryo-EM and cryo-ET are allowing us to visualize minute details, such as the precise tilting angles of the ribosome during elongation. Another major direction is the utilization of ribosome profiling, which has allowed us to visualize ribosomal stalls and collisions at a genome-wide level (which was previously not possible at all). The conference was a great reminder, though, of the specialized nature of our niche. So much of the translation field remains unexplored because of the deep regulation at each step of the process, and it was stimulating to see the different questions that hundreds of labs across the world brought to Heidelberg.

Naturally, it was very exciting when my protein of interest, eIF2, an essential translation initiation factor, or techniques that are performed in our lab (e.g., polysome profiling, ribosome profiling, etc.) were mentioned. The engagement from the community and other researchers around my own work and MEHMO Syndrome was also high. My poster presentations led to meaningful discussions ranging from foundational biochemistry to specific suggestions for future experiments. It was great to get feedback

from those that are experts in my field, and it was even better to be able to share with those experts the project that I'm so passionate about.

The experience wasn't all confined to the double-helix ATC, however. During a sightseeing afternoon in the historic streets of Heidelberg, we came across the statue of Robert Bunsen. Unveiled in 1908, it stands as a tribute to the man who gave us the Bunsen burner and chose Heidelberg as his lifelong home. Standing before a pioneer of the past while participating in a conference defining the scientific future was definitely a moment I'll never forget. I highly encourage anyone interested in protein synthesis to attend the EMBL Conference on Protein Synthesis and Translational Control or its sister conference at the Cold Spring Harbor Laboratory and learn more about the "Waltz of the Polypeptides."

San Diego International Conference on Child and Family Maltreatment

San Diego, California
January 26-29, 2026

SIERRA MARTIN
Center for the Study of Traumatic Stress

This January, I attended the 41st Annual San Diego International Conference on Child and Family Maltreatment (SDICCFM). As a research coordinator at the Center for the Study of Traumatic Stress (CSTS) in the USU Department of Psychiatry, this was an excellent opportunity to learn more about research, policy, and practice related to child maltreatment. In a lightning presentation entitled IPV Exposure and Bullying Victimization/Perpetration in Youth: A Nationally Representative Analysis, I presented results from a population-based analysis indicating that children's exposure to parental interpersonal violence (IPV) was associated with increased risk for bullying perpetration and victimization.

Results from subsequent moderation analyses suggested that interventions for childhood IPV exposure that do not take contextual factors into account may overlook high-risk subgroups for whom relative impacts of IPV exposure on social behavior are less evident. Accordingly, I enjoyed many stimulating discussions about implications for trauma-informed intervention in the days that followed.

As SDICCFM is a four-day conference attended by thousands of professionals who interface with victims of child maltreatment or family violence, my learning extended well beyond these topics. Every panel that I attended, from those discussing the impacts of disrupted attachment on sleep disorders to the effects of competitive sports on children's mental health, provided new insights into the field of childhood trauma.

One of the most illuminating sessions in this regard was entitled News You Can Use, which highlighted recent advances in the field of trauma and mental health research. The most striking research studies cited analyzed the rapid increase in prevalence of psychosocial disorders among U.S. youth over the past decade. Notably, though these trends may be partly attributable to problematic social media use and worsening parental mental health, the speakers acknowledged they may also reflect increased recognition and reporting of mental health concerns. This framing added important nuance to current discussions in the field about the origins of this crisis and strategies for addressing it moving forward.

Beyond external presentations at SDICCFM, I also enjoyed watching USU Research Assistant Professor of Psychiatry Dr. Christin Ogle present her work on domestic abuse and child maltreatment in military families. Using a population-based sample of 618,101 families across all service branches, her results demonstrated that children in active-duty families with a documented incident of domestic abuse are 2 to 11.5 times more likely to have a documented incident of child maltreatment as well. Above all else, I loved seeing CSTS' work with military populations so well-received by a wider audience. The number of child maltreatment professionals who approached Dr. Ogle to discuss future avenues for collaboration made me feel proud to belong to such a well-regarded research institution.

Overall, I am immensely grateful to CSTS and USU for supporting my attendance at SDICCFM. The lessons I learned from this conference were invaluable for my professional development, and I cannot wait to apply such insights to my work at CSTS moving forward.

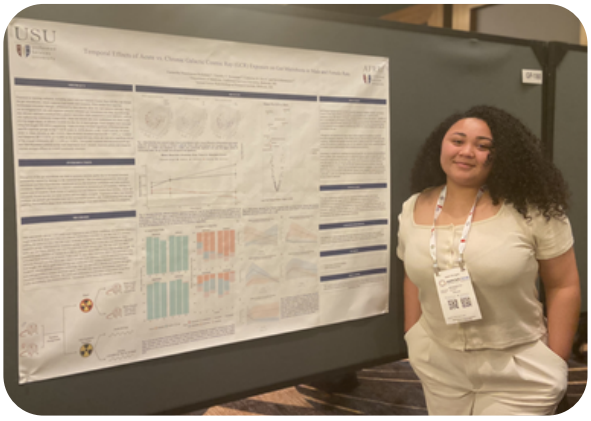
ANNUAL BIOMEDICAL RESEARCH CONFERENCE FOR MINORITIZED SCIENTISTS

ZAMANTHA MANALANSAN-ROBERSON
MCB PHD STUDENT

San Antonio, TX
November 19-22, 2025

I attended the Annual Biomedical Research Conference for Minoritized Scientists (ABRCMS) in San Antonio, Texas. ABRCMS is a large national conference that brings together thousands of trainees, faculty, and researchers from a wide range of biomedical disciplines. What makes this conference stand out is how trainee focused it is. There is a strong emphasis on mentoring, professional development, and creating space for students at all levels to share their work and grow as scientists.

As a first-year graduate student, attending ABRCMS was an incredibly positive and motivating experience. It was the first time I presented my graduate research at a national conference, and the environment felt supportive rather than intimidating. The poster sessions were well attended, and I received thoughtful questions and feedback from both peers and senior scientists. Those conversations helped me think more critically about my project and where it could go next.



My poster focused on temporal microbial community shifts in male and female rats exposed to different fractionation schemes of galactic cosmic ray (GCR) radiation, which is a collaboration between the Davis-Takacs and Burmeister labs. I presented the technical workflow I recently learned, which included isolating DNA and performing barcoded PCR amplification of 16S rRNA for long-read sequencing. The amplified products were sequenced using Oxford Nanopore Technologies flow cells on a GRIDion instrument. The GRIDion is a benchtop sequencing platform that allows multiple flow cells to run at the same time and generates long-read data in real time. After sequencing, I used the EPI2Me bioinformatics platform to perform downstream analysis and characterize changes in microbial community composition. While the project is still ongoing, early results suggest that radiation exposure disrupts gut microbial communities, supporting the idea that radiation negatively impacts gastrointestinal health.

In addition to my own research, I learned a lot from talks focused on microbiome research and overall gut health. A major theme across many presentations was the use of longitudinal and multi-omics approaches to better understand how biological systems interact and respond over time to environmental stressors. The field seems to be moving toward more integrated and translational research, and more specifically applies to our project since it can be related in the context of long-duration space travel.

One fun personal highlight was getting to explore San Antonio with other trainees after conference sessions. Some of the best scientific conversations happened outside the convention center, often over tacos along the River Walk, which made the experience feel both meaningful and memorable.

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Acknowledgements

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