PROBING THE MYSTERIES OF TRAUMA

Through innovative data-gathering systems, a UVM trauma physiologist turns the Emergency Department into a living laboratory.

by **Josh Brown** | photographs by **Mario Morgado**

> “Dr. Freeman has been able to develop an outstanding research program for emergency medicine and trauma using a novel model of student research assistants.”
>
> — **Steven Leffler, M.D.,** UVM Professor of Surgery and Chief Medical Officer, Fletcher Allen Health Care

Helen White,* a twenty-three-year-old skateboarder, grits her teeth and lets out a deep grunting moan. Her knuckles look like hamburger meat. She has black flakes of blood on her lower lip and around her nose, a curving laceration across her forehead, and two glistening gashes in her knee.

A white-and-orange cervical collar holds White’s head still, but her eyes move back and forth as two EMTs in green jumpsuits wheel her into a room on the main floor of the Emergency Department of Fletcher Allen Health Care in Burlington.

Kalev Freeman, M.D., Ph.D., leans over the stretcher to look White in the eye. “I’m Doctor Freeman. You’re going to be okay,” he says very gently, as a team of nurses and technicians pull up trays of supplies. “We’ll get you feeling better here.”

Freeman turns to one of the nurses, Sheena Fisher, R.N., who is adjusting an IV line. “Let’s do a hundred of fentanyl,” he tells her and then turns back to his patient. “We’re getting you some medicine to help with your pain.”

The EMTs report that White collided with a streetlight and fell, face-first, over a small concrete wall in downtown Winooski. No helmet. “Where are you hurting, my friend?” Freeman asks.

“My head hurts so bad,” White tells him, groaning again, and her eyes drift up to a monitor overhead, beeping out a record of her breaths and beating heart. “I’m looking to see what needs stitches,” he says, peering closely at his patient’s forehead. But Freeman is more concerned about what he can’t see: what might be happening inside White’s skull.

“Are you able to sit still for a few pictures?” he asks. “We’re going to take some pictures of your head and then we’ll get you stitched up.” White grunts and gets whisked down the hall for a CAT scan.

Just outside White’s exam room, recent UVM graduate Chelsea Manning, who’s now working as a research assistant in the Department of Surgery, has been waiting quietly. She’s holding a vial for collecting blood. Freeman steps out to talk with her. “We are going to draw blood from her for the study,” Freeman tells Manning. “We’ll enroll her. I think she’s going to get admitted. Head bleeding? Could be. I’m guessing she broke some of the bones in her face. She’s pretty crunched.”

Then he sits down at a bank of computers to order some tests for his new trauma patient. A surgeon strides by in blue scrubs. More EMTs wheel around the corner with a bed, pushing an elderly patient the color of ash. Like a chorus of electronic frogs, there’s a constant beeping and ringing in the air from telephones and monitors.

It’s not exactly the quiet, peaceful environment a scientist might hope for to do research, or a professor might hope for to instruct college students.

But Freeman, who is an assistant professor of surgery and pharmacology, director of Emergency Medicine Research, and the lead investigator of the Trauma Physiology Laboratory at the UVM College of Medicine, does both. He conducts research and teaches undergraduates and medical students — right in the emergency room.

In return, his research on trauma — particularly traumatic brain injury and blood clotting — depends on the 24-hour-a-day, 7-days-a-week efforts of undergraduate students (and a few recent graduates, like Manning) enrolled in two courses he founded: Surgery 200 and 201. Since 2008, he’s had hundreds of students — in four-hour shifts as the required lab for the courses — working alongside him and other doctors in the emergency room, screening and enrolling patients for clinical studies. “They’ll be here at 3 a.m. on a holiday weekend,” he says.

Freeman received his undergraduate degree from the University of Michigan before earning his M.D. and Ph.D. from the University of Colorado and performing a residency in emergency medicine at Boston University. When he arrived in Vermont in 2007, he approached Steven Leffler, M.D., then head of UVM/Fletcher Allen’s Division of Emergency Medicine, who is now the chief medical officer for Fletcher Allen. “I knew that there was a very strong clinical program in emergency medicine, but almost no research arm,” Freeman recalls. “My first love is science, and I told Steve I thought I could set up a trauma research program with a shoestring budget.” Leffler wanted to know how. Modeled on a program at the University of Pennsylvania, Freeman told him, “My plan is to build an infrastructure using undergrad students as a team.”

Unlike most medical schools and Level 1 trauma centers, UVM and Fletcher Allen are surrounded by undergraduate students, with many pre-med and science students eager to get experience in a clinical setting. Several UVM dorms literally look out on ambulances arriving at the emergency department. “We have this unique pair of institutions in Vermont where we have undergrads right around us. Let’s tap in to this motivated young workforce and have them help us,” Freeman told Leffler, who helped him get started.

So far, the students have gathered data for 22 studies, both for Freeman and for other researchers across the College of Medicine.

Leffler is impressed by what Freeman has built. “He has been able to develop an outstanding research program for Emergency Medicine and Trauma using a novel model of student research assistants.

At left, a Fletcher Allen Emergency Department team practices the kind of trauma situation that results in a blood sample collection. Chelsea Manning, above, collected samples and data both as a student and a research assistant.

* Helen’s name and case details have been changed to protect her privacy.

This innovative program has been great for our patients, academic medical center, and the students."

With this team, Freeman's research aims to understand the relationship between traumatic injury and blood vessels. Several of his studies focus on the endothelium — the inner lining of blood vessels that regulates smooth muscle, helps form blood clots, and provides a barrier to fluid that could leak in the brain. But in trauma the biochemical signals in the endothelium can go haywire, Freeman believes, which leads to a cascade of other medical problems.

Many physicians think of trauma as a mechanical problem requiring a surgical fix. Broken bones can be set, amputated limbs reattached, lacerated skin stitched. But brain damage from swelling and the failure to effectively form blood clots are complex problems of vascular biology that defy surgery. They're problems that involve the endothelium — and they're two of the primary reasons people die after severe trauma.

Every 23 seconds someone in the U.S. sustains a traumatic brain injury, the Centers for Disease Control and Prevention reports — about 1.7 million people each year, resulting in 52,000 deaths. Many of these deaths come hours, days, or weeks after the initial trauma and are often triggered by failure of other body systems outside the brain. "There is a fundamental knowledge gap in our understanding of the long-term impact of

Kalev Freeman, M.D., Ph.D., reviews imaging of a possible head trauma with UVM student research assistant Heidi Considine in the Fletcher Allen Health Care Emergency Department.

acute brain injury on systemic endothelial function," Freeman writes. In other words, when a car crash victim with a head injury dies of a heart attack a week later, it may be because "the cardiac tissue was damaged by brain trauma. All the blood vessels are affected by the stress of a brain injury," Freeman says.

And there's a similar lack of knowledge about uncontrolled bleeding, one of the major causes of mortality in trauma. Of U.S. soldiers injured by combat, most of them — 88.9 percent according to the Army Institute of Surgical Research — die on the battlefield. But of those combat injuries that were "potentially survivable," Freeman says, more than 90 percent of soldiers who die simply bleed to death. For some reason, many severely wounded people can't form blood clots — and Freeman would like to know why.

"You'd think we could just give these patients blood transfusions. No one should ever die from bleeding, because we can give them blood!" Freeman says. "But they just can't make a blood clot." There are several theories about why this happens: massive infusions of red blood cells and plasma change the biochemistry of the blood's natural clotting mechanisms. Saline infusions dilute blood proteins. Dropping body temperature and build-up of acid may contribute. Genes matter. Freeman would like to show how dysfunction of the endothelium is also a culprit.

"We've already figured out most of the possible surgical procedures for trauma, but sometimes you stitch up all the holes and they're still bleeding out and there's not much you can do about it," he says. "What is there after mechanical surgery?" Freeman asks. His answer: "Better biochemistry."

"If we can understand what is going on with blood vessels after trauma," Freeman says, "then we can target therapies to help protect them and thereby benefit blood clotting capabilities and prevent brain swelling."

"If we can understand what is going on with blood vessels after trauma, then we can target therapies to help protect them and thereby benefit blood clotting capabilities and prevent brain swelling."

— **Kalev Freeman, M.D., Ph.D.,** Assistant Professor of Surgery and Pharmacology, Director of Emergency Medicine Research

That's why, just before midnight, Chelsea Manning is still waiting outside of Helen White's examination room. The patient has returned from her CAT scan and Manning is hoping that a technician will soon return her vial, filled with White's blood. If White gets admitted to the hospital overnight, she'll qualify for one of the trauma studies Freeman is helping to lead, with a team of other researchers and universities, on the biochemistry of blood clotting. Manning's job as one of Freeman's student "chiefs" — having completed the two surgery courses and now working for him before applying to medical school — is to take the blood from the technician and go to a tiny lab just off the trauma bay in the ER. There, she'll prepare it for study, to see how fast and firm it clots.

"Most of the time there would be another student here to collect the blood sample, and I'd be prepping everything back in the lab, but since I'm on by myself tonight I'll do both," she says. The study, led by UVM biochemists Kathleen Brummel-Ziedins, Ph.D., and world-renowned blood expert Kenneth Mann, Ph.D., aims to get a clearer sense of the natural history of coagulation in trauma patients. Their goal: start to develop profiles and possible biomarkers for people who are going to have coagulation problems. Some clot too easily; some don't clot well at all. "Trauma surgeons would love to have this information," Freeman says, "before they begin to operate."

While Chelsea Manning waits, Freeman and a medical student sit in the blue gloom of an image viewing room, looking at glowing scans of Helen White's head and spine. "The big risk for her is bleeding. She's gotten facial trauma, so I'm looking to see if she's got any blood inside the skull," he says, as he scours the ghostly grey images for telltale bright-white patches behind the eye sockets or between bone and brain. "You can see she broke her nose here," he says pointing to an unhappy-looking angle in the picture. "But I don't see any threatening bleeding in the skull," he says. "That's good."

A few minutes later, Manning steps in the room. "I'm ready to do the blood," she says. "I'm on call all night; do you want me to stay with her and do the two- and four-hour draws? Do you think we're ultimately going to use her blood?"

"I'm not sure if she's going to have an admission injury," Freeman says, "but let's go ahead and run the blood sample and get this piece of data and log it. I'll know before midnight."

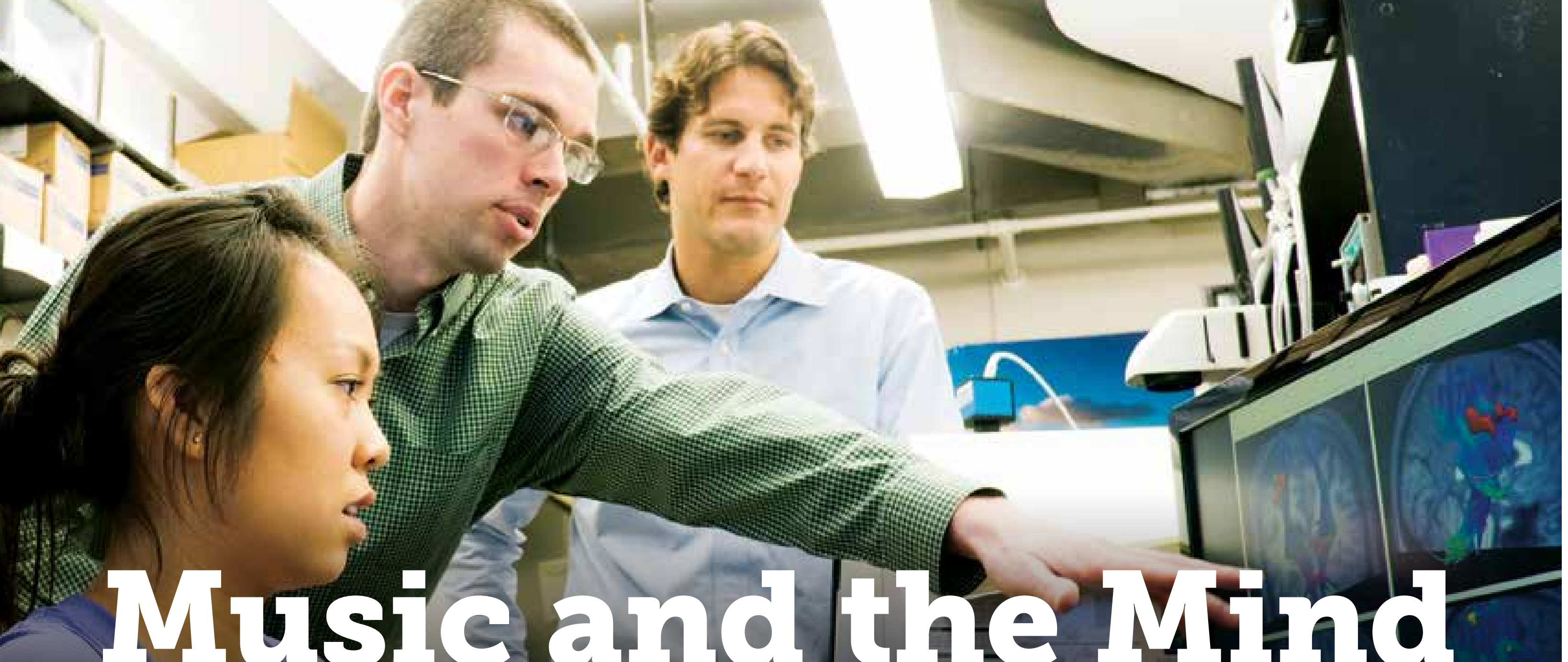

Research assistant Abby Wager prepares blood samples as Dr. Freeman observes. Because blood from trauma victims must be processed soon after their injury, Freeman built an analysis facility in a former closet at the Emergency Department.

In the little lab, Manning spins the blood in a centrifuge and then runs samples into two machines that will measure its clotting characteristics. "Here we can see how quickly it clots," she says. On a computer screen a thin line spreads out into a wide blue band. "That's where the clot is starting," Manning says, as the data streams out, forming a bell-shaped pair of curves, beautiful and orderly.

Trauma, on the other hand, is, almost by definition, disorderly and unpredictable. A blinding rush of headlights. A leg blown off by an IED under your Humvee. A sudden rending of our gossamer plans by an intrusive, painful snap. "This is why we haven't figured out the answers to many trauma questions, because it is so challenging to study; you can't plan for it," Freeman says, "These are people in the worst of circumstances, in the middle of the night, and we have to work fast. It's very hard to get this data. It's simply a feasibility challenge. An emergency room is a very difficult environment to do robust scientific research."

An additional challenge: Freeman needs Helen White's permission to participate in this clotting study. Informed consent is a foundation of all ethical medical research. But how do you get consent from a patient who just smashed her face on the concrete? Or worse. "When someone is bleeding out from everywhere and they're on a ventilator, how can you get them to sign a consent form to take a blood sample?" Freeman asks.

You can't. And yet understanding what's happening with critically injured patients — just after they're injured, in real time — is some of the most important work in emergency medicine. That's why Freeman developed special protocols with the ethics committees of the university and hospital. He got permission to get a waiver of consent to take an initial blood sample from trauma patients. "Then we don't do any analysis or reporting on that data until we go back to the patient and get their permission," Freeman explains, "once they've recovered." If they've died? "We go to a family member and we've got thirty days to get consent from the family."



Music and the Mind

When a soccer player with a concussion comes into the emergency room at Fletcher Allen Health Care, medical student ALEX THOMAS'17, would like to catch him. And, maybe, encourage him to listen to music on his iPod.

Throughout his undergraduate years at UVM leading up to his entrance into the College of Medicine, Alex Thomas has been helping a team of researchers led by Professor of Psychiatry Magdalena Naylor, M.D., Ph.D., and emergency medicine specialist and Assistant Professor of Surgery Kalev Freeman, M.D., Ph.D. — who are working together to better understand what's happening in the brains of patients suffering with mild traumatic brain injuries. Naylor and Freeman are also testing the idea that people with concussions might recover better and faster with mindfulness training — a cognitive-behavioral therapy — that uses music as a focusing tool.

Of the 1.7 million traumatic brain injuries in the United States annually, about 1.4 million are mild, otherwise known as concussions.

Top: Kalev Freeman, M.D., Ph.D. works with medical student Alex Thomas'17 and UVM student research assistant Tram Tran. Above: Professor of Psychiatry Magdalena Naylor, M.D., Ph.D.

Concussions can produce a range of symptoms such as headaches, depression, slowed reaction times, memory loss and sleep problems. But beyond these cognitive, behavioral and emotional clues — often self-reported — there is no method of detecting a head injury in mild cases.

In 2011 and 2012, Thomas and other students taking Freeman's Surgery 200/201 courses helped recruit patients with concussions to be part of the Head Injury Testing and Outreach Program (HITOP). Using an advanced MRI machine near the Emergency Department, the researchers tested 28 of these volunteers soon after their injury and then seven days later using a state-of-the-art technique called diffusion tensor imaging

The team has been looking at the brain's white matter — axons — to see if shearing or swelling can be detected, giving a new view on mild brain injuries. This imaging is very sensitive, and the team hopes to detect damage of fibers where other techniques can't. The study also tested the patients' brains at work, using functional MRI imaging, looking at blood oxygenation levels in several areas of the brain's gray matter while the patient worked on, for example, a memory task.

On both types of imaging, the researchers found significant differences between control patients and those with concussions. Another important finding: in the hours right after a concussion, many patients have the same symptoms — but the research team saw low activation of brain areas associated with memory tasks in the patients who didn't recover quickly from their injury, Thomas reports, "whereas there is high activation in those who will go on to recover and the control group."

In other words, in addition to finding physical evidence of concussions, the researchers hope that this study may point toward techniques that would be predictive of who is likely to go on to have long-term symptoms — or develop the post-concussive syndrome increasingly seen in NFL players and recent combat veterans.

Those patients who still had symptoms after a week were invited into the second stage of the study: a six-week program of mindfulness training supervised by Naylor, who directs UVM's Mind/Body Medicine Clinic. The patients met once a week to learn meditation and focusing techniques that the researchers believe can help injured brains recover.

A major focus of the sessions: cognitive exercises with music. Young men are major sufferers of concussions, but they are much less likely than women to participate in traditional group therapy. "It's tough getting NFL guys to sit in group therapy," Freeman says, "but iPod therapy could work. These are cognitive exercises, focusing, for example, on certain sounds like a horn or drum beat. It's like a mind gym."

One could be forgiven for imagining Kalev Freeman saying, "I'm only a real doctor; I don't play one on TV." His blue eyes, athletic chin, impish smile, and Gen-X tattoos, barely visible beneath a short-sleeved shirt, might make the cut in Hollywood. And after hearing his slow, guffawing laugh, one could see how he considered a different career as a bluegrass fiddler. But spend more time with the man and it becomes clear that here is someone with remarkable drive and sense of mission.

"When you're in the hospital, it's like running the marathon," Freeman says. (He would know, having run several editions of the Vermont City Marathon, including one where he finished an overnight shift in the emergency room at 7 a.m. and toed the starting line downtown at 8 a.m.) "It's a very high-intensity activity and I can forget about my lab work while I attend to patients."

But most days, Freeman wakes up thinking about his next experiment, he says. And most of his time, other than his four shifts a month in the Emergency Department, is spent on the third floor of the Given Building, conducting animal studies on the physiology of brain injury. Unlike the emergency room, the lab is predictable and the work methodical. "You can always count on the rats to be there at 10 a.m.," he says.

He can also count on several hard-working students too, like Tram Tran (UVM'13) and Alex Thomas, a Class of 2017 medical student. "As a freshman in the UVM Honors College, Tran contacted Freeman to see if she could help in his lab. He put her to work right away, and, four years later, she has become a star biochemistry student, completing her undergraduate thesis under Freeman's supervision and preparing to apply to medical school. "He's amazingly dedicated to his students," says Alex Thomas.

Above all other tasks, the body seeks to send the right amount of blood to the brain, feeding its delicate oxygen-gulping network of vessels, neurons, and memories.

Whether sleeping or sprinting, the healthy body has an amazing ability to keep constant blood flow to the brain.

Testing brain and gut arteries from animal models, Freeman and his students are exploring how the molecular signaling mechanisms in endothelium, particularly calcium pathways, can misfire after a traumatic brain injury — leading to excessive dilation in the brain and blood vessels. With his mentor, University Distinguished Professor Mark Nelson, Ph.D., chair of the Department of Pharmacology, Freeman has been collecting data showing that endothelial cells are hyperactivated following trauma, as a wave of calcium ions move in. This blast of calcium could be a cellular foundation for both swelling of brain tissue and loss of clotting capacity.

Using high-speed video images from powerful spinning-disc confocal microscopes in Nelson's nearby lab, Freeman and his team can observe and measure calcium, nitric oxide, and other signals that move into and through endothelial cells. Their hope is to help point the way toward treatments that could block key calcium ion channels, turn off overabundant calcium signals, and maintain clotting pathways: in short, calm the endothelium. In the long run, Freeman would like to contribute to long-sought therapies for uncontrolled bleeding and traumatic brain injuries.

But this night, in the hospital, it's approaching 1 a.m. Freeman talks

At top: frequent group meetings give the large research team a chance to share findings. Above: student presenters compare notes before the start of a group meeting.

animatedly to a radiologist on one of several phones he's assigned in the emergency room. Helen White, it turns out, is not going to be admitted as an in patient to the hospital. Her injuries hurt, but they're not as serious as they first looked and her head now seems fine. Some stitches, wound scrubbing, pain medications, and she'll be heading home. "We got the first blood sample, which we can use in the comparison group," Freeman tells Manning. But because the patient is being discharged, she can't be in the main trauma study. And in that, Helen White, lacerated, sutured, and sore, could count herself fortunate.

"I work in the lab all week," Freeman says, "Then I go work a shift in the E.D. and see someone on Friday night, someone in a car accident, with the same injury that we're modeling and studying. That brings it home. It reminds me why we're doing the research." VM