Head Hits

UM research uses biomarkers to reveal brain injuries

Hard knocks: ***UM soccer player Payton Agnew (left) goes for a header during a 2015 match against the Purdue Boilermakers. The student-athlete has volunteered to aid UM researchers who study concussions.*** *(Photo by John Sieber)*

By Andrea Lewis

UM soccer player Payton Agnew's world was jolted on Oct. 10, 2014. Her memory of that day isn't crystal clear, but one thing remained in focus: Her season was over.

The Montana Grizzlies were clad in pink that day in honor of breast cancer awareness. Their opponent was the University of Idaho. Agnew, a redshirt sophomore from San Diego, entered the game. She hadn't even touched the ball when her teammate got a free kick. Agnew, being tall, moved into the box, and her teammate kicked it directly to her. Agnew leapt for the header. Unfortunately her opponent did the same with elbows out, came crashing down onto Agnew and rammed an elbow into her face.

Her memory of what followed is spotty. She lay on the field, unable to move. UM trainers mobilized and immediately took Agnew off the field and out of the game. Her eyes were extremely sensitive to light, her balance was off and a wave of nausea washed over her. She'd experienced these symptoms before. She was certain she had a concussion.

What wasn't certain was the severity of her mild traumatic brain injury.

Two UM researchers in the Skaggs School of Pharmacy are working to change that. Research Assistant Professors Sarj Patel and Tom Rau have made some exciting discoveries, which they hope will lead to a test that can definitively measure whether someone has a mild TBI, assess its severity and objectively measure recovery from the injury.

When Agnew was taken off the field, her trainers ran her through the Glasgow Coma Scale, which is a subjective measure of level of consciousness based on response to various stimuli.

"When you get into mild concussions, or TBI, it's very difficult for the Glasgow Coma Scale to pick up real subtle differences in a patient," Rau says. "So, there has been a movement in the field of diagnostics to assess mild patients in an objective manner."

And that's exactly what their research team is doing. The group includes senior staff scientists Diane Brooks, Eric Wohlgehagen and Fred Rhoderick, as well as physical therapy Assistant Professor Alex Santos. They are working to develop a biomarker in the blood that indicates how the brain reacts following a traumatic brain injury.

"Ultimately we want to say, 'OK, this person *did* have a concussion and six weeks later is completely recovered,'" Rau says.

Currently, recovery is assessed using neuropsychological measures – which largely are based on the intelligence of the individuals. Even though patients can pass the tests, they may not be fully recovered.

UM Intercollegiate Athletics employs the ImPACT model, which is a series of assessments that involve cardiovascular stressing and cognitive measurements using the standard Sport Concussion Assessment Tool, or SCAT3. This is what was used to evaluate Agnew's recovery. While SCAT3 protocol is among the best, Rau says it's risky. There can be a huge learning curve where athletes learn to memorize the questions and responses, so it's not a true, objective measure of recovery.

"I took the SCAT3 countless times," Agnew says when explaining her road to recovery. "I took it enough times I had all the numbers, all the words and questions memorized to where they had to start creating new questions for me."

The research duo joined forces in a quest to develop a clinical lab test for TBI patients that can justly measure recovery before health care providers give the green light to resume normal activity. Their scientific expertise is a great match. Rau is an acute neural injury expert, and Patel is a pharmacology expert. Their meeting of the minds happened somewhat by happenstance, but when the two decided to put their heads together, they saw promising results.

So what's behind the science? Patel explains that by measuring blood-based biomarkers they are measuring micro-ribonucleic acid, or RNA, which are very small pieces of nucleic acid that very powerfully regulate how proteins are expressed in the body.

"What we've found with our work is following injury there is an increase of these micro-RNA molecules in the blood of the patients," Patel says.

Their hard-hitting data caught the eye of two high-profile companies – the National Football League and General Electric Co. – which are investing in leading research to improve the safety of athletes, members of the military and society overall.

In January 2014, the team's seed money was running out. The researchers were preparing to pack up their offices when they got word they had been selected as one of 16 winners in the first stage of GE/NFL's Head Health Challenge I. They received

$300,000, mentorship and access to GE researchers and industry thought leaders. In 2015, they would have an opportunity to win an additional $500,000 award.

"The first award allowed us to immediately begin research to identify biomarkers of injury occurring in the brains of athletes or military personnel," Patel says.

Their aim was to collect blood samples from people who had suffered from a traumatic brain injury. When they were looking for test subjects, one of the partnerships they formed was with UM Head Athletic Trainer J.C. Weida.

"That initial study was predominately with UM athletes," Patel says.

During their annual physicals, Weida alerted all football and soccer players of the opportunity to be involved in the study. Those who elected to participate had their blood drawn. Then if the athlete suffered a concussion, they could choose to have their blood drawn within 48 hours of the injury. The researchers collected and examined the samples, looking for the biomarkers to show up in the blood.

Agnew was one of the players who agreed to participate.

"We just want to help out," Agnew says. "We know what a unique opportunity it is to have this kind of research [at UM]."

The researchers got to work comparing the biomarkers in the control sample to the biomarkers in the blood of TBI sufferers. Some of these markers mirrored the patterns they observed in the animal model. The researchers were encouraged, but they wanted to know more.

The topic of brain injuries has become a high-profile issue highlighted by a large number of former NFL players, among others, being diagnosed with a neurodegenerative disease called chronic traumatic encephalopathy, or CTE. Recent findings show people who suffer numerous brain injuries or get a second TBI before they are fully healed from the first experience long-term effects on the brain.

Rau and Patel decided they would expand their study to see if the biomarkers could be observed in people who suffered from CTE as an end-stage disease. They formed a partnership with the brain bank at Boston University and obtained tissue samples. They were pleased to find the familiar markers from their previous studies also observed in the postmortem human tissue.

Researchers Alex Santos, Tom Rau and Sarj Patel *(standing left to right)* ***test the extent of brain injuries using equipment that tracks the eye movements of subjects.***

"We gave [GE/NFL] twice as much data as we originally promised," Rau says. "It was a hard year, but we knew we had one shot at it, and we wanted to dazzle them."

NFL and GE were impressed. "The fact that we were seeing very similar changes in the markers really pushed home that story for them," Patel says.

At the end of July, Rau and Patel received a phone call informing them they had been selected for the final round of funding. The small UM team was among six other final winners nationally selected from the initial group of 16 to receive a second-round, $500,000 grant.

The current award will allow the research team to clinically validate the research – both in TBI and in CTE. Because proteins work in the body as transporters and catalysts, a disruption in one area could cause further-reaching problems. The research may help solve the mystery of why a localized brain injury causes damage throughout the entire brain.

"The workday never ends, but that's OK, because we are chasing down a dream," Rau says.

Part of that dream is to create diagnostic tools that will directly benefit TBI patients. In August 2015, the research team earned $2 million in follow-up funding from the state and the Montana University System. Using their GE/NFL findings as a launch-point, the team will collaborate with other TBI researchers and private companies to make their dream a reality.

"We want our research to improve health, create jobs and generate revenue for Montana," Rau says.

"We've got to get it right since we are one of the first," Patel says.

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