Stem Cell & Regenerative Medicine Center
UNIVERSITY OF WISCONSIN–MADISON

2019 Update

Randolph Ashton, Ph.D., associate professor of biomedical engineering, became our new SCRMC Associate Director last November. He joined SCRMC Director Timothy Kamp, M.D., Ph.D., professor of medicine, cell and regenerative biology, and succeeded William Murphy, Ph.D., professor of biomedical engineering and SCRMC Co-Director 2012-2018.

Ashton joined the UW–Madison College of Engineering faculty in 2011, setting up his lab at the Wisconsin Institute for Discovery. He has since served on SCRMC's executive committee and helped advance the center's training and educational programs. He has presented in the SCRMC's weekly seminar series, as well as its student-organized fall conference and has co-chaired the Wisconsin Stem Cell Symposium.

Randolph Ashton, Ph.D.

Among Ashton's many honors are the College of Engineering's 2018 Equity and Diversity Award, the 2017 National Science Foundation CAREER Award, and the Young Investigator Faculty Award at the 2016 Regenerative Medicine Workshop. Ashton has published in *Nature Neuroscience, Biomaterials, Stem Cell Reports* and other prestigious journals. The Wisconsin Alumni Research Foundation has filed five patent applications on technologies developed in his lab.

Ashton's lab develops novel tissue engineering methods to derive brain and spinal cord tissues from human pluripotent stem cells. Researchers use the cells to explore regenerative therapies and bioengineered tissues to investigate neurological disorders and evaluate neurodevelopmental effects of pharmaceutical and chemical compounds used in everyday consumer products.

Ashton has been busy working with the center's executive committee, staff and faculty to chart the course of the SCRMC. The center helps facilitate the research of more than 100 faculty members working across six UW–Madison schools and colleges, 40 departments, and 10 centers and institutes. Close to 700 faculty, staff and students work, teach and study in the field at UW–Madison.

"I am honored to serve UW–Madison in this capacity, and give back to a research community that has greatly benefited my lab's trainees and research," Ashton says.

"Randy is a leading stem cell scientist on campus who will strengthen the interdisciplinary efforts of the SCRMC," Kamp says. "His collaborative spirit and productive research program make him a wonderful new associate director for the SCRMC."

Research highlights from SCRMC faculty

Following are selected research highlights from the past year from UW–Madison scientists who are also SCRMC faculty members helping to advance research, collaboration, training and education in the field.

December

Peiman Hematti, M.D., bone marrow transplant physician at the University of Wisconsin Carbone Cancer Center and director of the Clinical Hematopoietic Cell Processing Laboratory, is the site principal investigator for a new clinical trial using stem cells derived from the umbilical cord blood of newborns to treat patients with acute myeloid leukemia. The hope is that this new cell therapy will help prevent infections and keep patients healthier as they go through chemotherapy. The UW Carbone Cancer Center is one of 36 cancer centers worldwide to test the new treatment.

February

The UW Program for Advanced Cell Therapy (PACT) will also conduct a study to examine a therapy to treat a viral infection faced by up to 50 percent of bone-marrow transplant recipients. The study will deploy virus-specific white blood cells to treat lethal cytomegalovirus (CMV) reactivation that can occur after a bone-marrow transplant. The FDA-approved trial will begin enrolling adult and pediatric patients immediately through a partnership with UW Health, according to Inga Hofmann, MD, PACT medical director and principal investigator. She is working with PACT Director Jacques Galipeau, M.D. *(at right)* on the trial.

March

Emery Bresnick, Ph.D., professor of cell and regenerative biology, reported in the Journal of Clinical Investigation that the transcription factor GATA-2 is a critical regulator of hematopoietic stem and progenitor cell (HSPC) development and function, and mutations in the enhancer region of GATA2 are linked to blood disorders. Bresnick and colleagues developed and characterized a mouse model that harbors a human disease-associated GATA2 enhancer mutation. In their model, hematopoietic development and function were normal unless the animals were exposed to a secondary stress that necessitated blood cell regeneration. The results of this study provide important insight into GATA-2-dependent pathogenesis.

April

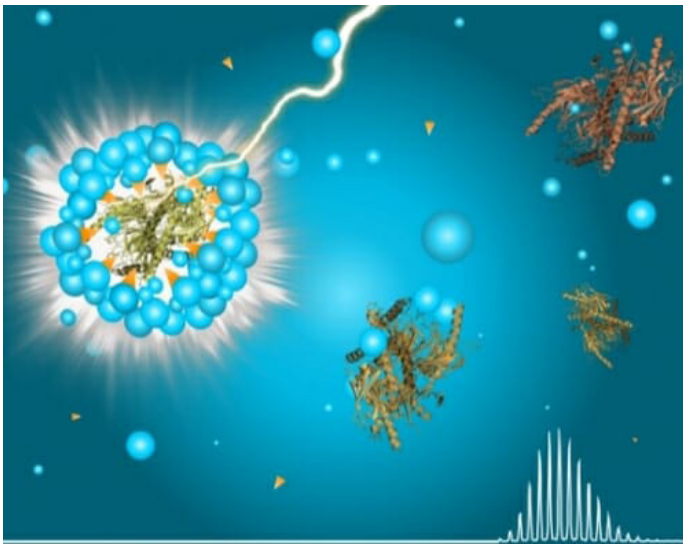
Ray Vanderby, Ph.D., professor of orthopedics and rehabilitation, and Peiman Hematti, M.D., professor of medicine, pediatrics, surgery and biomedical engineering, are part of an interdisciplinary team of researchers at UW–Madison that has developed a promising new cell therapy with potential to improve tissue healing after orthopedic injuries. The new cell therapy, described in the journal *Stem Cells*, accelerated the recovery of ruptured Achilles

Jacques Galipeau, M.D.

Research highlights (continued)

tendons in a rodent model, and may similarly aid other healing tissues, shortening the time until these structures regain functional strength. The research team is now working to obtain FDA approval for a first human clinical trial to treat devastating injuries in musculoskeletal tissues.

Ying Ge, Ph.D., associate professor of cell and regenerative biology and chemistry, and her research team reported in the journal *Nature Methods* the development of a novel strategy capable of extracting and driving hard-to-reach proteins into water solution where they can be effectively studied using mass spectrometry, a powerful analytical technique. The new approach *(depicted right)* promises a trove of biological insights and, importantly, may help identify therapeutically relevant proteins and provide new disease diagnostic techniques.



A chemical surfactant or detergent used to help prepare protein samples for analysis by mass spectrometry, is cleaved in this illustration by ultraviolet light. Breaking the molecule eliminates it from samples, leaving only the subject proteins for analysis. (Artwork designed for this paper by graduate student Standford Mitchell.)

August

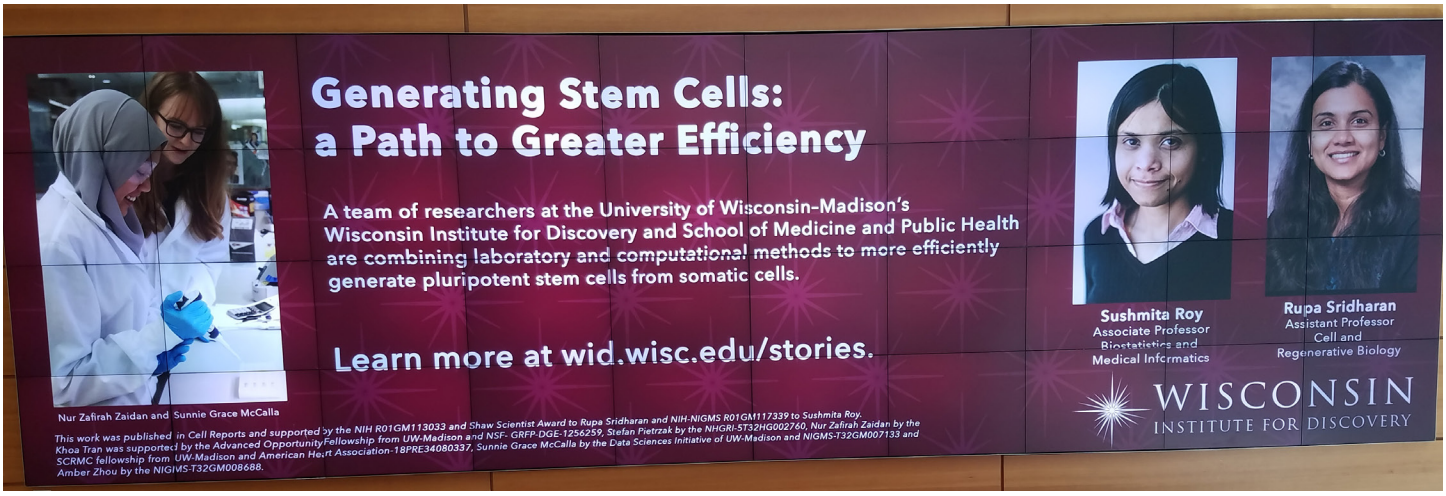
For the first time in the United States, a research team will test a personalized cell therapy to treat a common and serious complication facing kidney transplant patients.The UW Program for Advanced Cell Therapy (PACT), directed by Jacque Galipeau, M.D., professor and assistant dean of medicine at the School of Medicine and Public Health (SMPH) will study a therapy to treat a viral infection faced by around 30 to 40 percent of kidney and/or pancreas transplant recipients. The study will deploy virus-specific white blood cells to treat severe cytomegalovirus (CMV) infection after kidney transplant. The U.S. Food and Drug Administration-approved trial will begin enrolling 20 adult kidney-transplant recipients, according to Dr. Arjang Djamali, professor of medicine and surgery at the SMPH and UW Health nephrology division chief.

September

Tiny capsules packed with gene-editing tools offer an alternative to viral delivery of gene therapy, SCRMC research collaborators reported in the journal *Nature Nanotechnology.* These new tools for editing genetic code offer hope for new treatments for inherited diseases, some cancers, and even stubborn viral infections. The typical method for delivering gene therapies to specific tissues in the body can be complicated and may cause troubling side effects. The researchers have addressed many of those problems by packing a gene-editing payload into a tiny, customizable, synthetic nanocapsule. Collaborating on the research are SCRMC faculty members Shaoqin "Sarah" Gong, Ph.D., biomedical engineering professor and investigator at the Wisconsin Institute for Discovery; Krishanu Saha, Ph.D., biomedical engineering professor and steering committee co-chair for a nationwide consortium on genome editing with $190 million in support from the National Institutes of Health; Bikash R. Pattnaik, Ph.D., pediatrics and ophthalmology professor, and Masatoshi Suzuki, Ph.D., comparative biosciences professor.

SCRMC Fast Facts

- Close to 700 faculty, staff and students overall are working, teaching and studying in the field of stem cell and regenerative medicine at UW–Madison.
- SCRMC faculty members work across six UW–Madison schools and colleges, 40 departments, and 10 centers and institutes.
- In 2018-2019, stem cell research at UW–Madison drew more than $44 million in NIH funding. Additional funding comes from other federal government agencies, industry and philanthrophic sources.
- In the past decade, our scientists have published close to 1,198 peer-reviewed research articles involving stem cells.
- UW–Madison School of Medicine and Public Health funding and philanthropic gifts support the SCRMC's activities, such as funding pilot research grants, education and training for students, research support cores, events facilitating scientific collaboration, and public outreach.
- Nearly 33 clinical trials are underway involving human embryonic stem cells and their derivatives, intended to advance treatments for heart disease, diabetes, Parkinson's disease and more. Another 46 trials involve the use of induced pluripotent stem cells.
- The market for products from companies founded, license agreements and patents related to stem cell discoveries is projected to reach more than $270.5 billion by 2025.
- Our scientists have garnered more than 120 research patents and executed more than 70 commercial license agreements to 47 entities through the Wisconsin Alumni Research Foundation.
- Stem cells have been a boon for business, including in Wisconsin, where at least 10 companies rely on pluripotent stem cells. One of them, WiCell, is a Madison-based non-profit that has supported stem cell research on campus and beyond since 1999. WiCell employs 22 people at University Research Park and is a



SCRMC researchers collaborate across campus — to the west at UW Hospital, the Waisman Center, School of Veterinary Medicine and Wisconsin Institutes for Medical Research; on central campus at the Discovery Building's Wisconsin Institute for Discovery and Morgridge Institute for Research, the College of Engineering and McArdle Laboratory for Cancer Research; on south campus at the Wisconsin National Primate Research Center, and more. (Photo of rotating research highlights on the wall inside the Discovery Building by J. Lenon).

Researchers share their discoveries at the poster session during the annual Wisconsin Stem Cell Symposium at the BioPharmaceutical Technology Institute, co-organized each April by the SCRMC. (Photo by J. Lenon).

recognized global leader in characterization testing and distribution of stem cell lines. Its catalog has grown from 75 stem cell lines three years ago to almost 1,500 today. WiCell has made over 7,500 distributions to 2,711 investigators at 820 institutions in 45 countries around the world. Among the most requested are the original five lines that UW–Madison scientist James Thomson, V.M.D., Ph.D., now director of regenerative biology at the Morgridge Institute for Research, first derived 20 years ago.

Melissa Skala, Ph.D.
(Photo courtesy Morgridge Institute for Research)

SCRMC Faculty Honors

Judith Kimble, Ph.D., Vannevar Bush Professor of Biochemistry, received a WARF Named Professorship. Kimble discovered the first stem cell niche in 1981, and since has unraveled the genes, pathways and networks that regulate stem cell self-renewal and differentiation. Her research, based in nematodes, has revealed molecular mechanisms operating in all animals, with implications for human disease.

Weibo Cai, Ph.D., professor of radiology and medical physics, received an H.I, Romnes Faculty Fellowship. Cai studies molecular imaging, molecular therapy and nanobiotechnology. He has served on the editorial board of several journals and various committees of the Society of Nuclear Medicine and Molecular Imaging. He teaches molecular imaging.

Linda Schuler, V.M.D., Ph.D., professor of comparative biosciences, received a 2019 Hilldale Award for distinguished contributions to research, teaching and service. Among the first professors hired to inaugurate UW–Madison's School of Veterinary Medicine in 1983, her research with cow genetics led her to discover that the milk-stimulating hormone prolactin can induce breast cancer. Schuler, who now studies cancer stem cells, has focused on developing the careers and talents of new faculty and has also mentored more than 150 graduate students.

Melissa Skala, Ph.D., associate professor of biomedical engineering and principal investigator at the Morgridge Institute for Research, was named a fellow of both the American Institute for Medical and Biological Engineering (AIMBE) and SPIE, an international society for optics and photonics. AIMBE honored Skala for her work applying optical imaging to tumor metabolism and personalized cancer drug screenings. SPIE inducted Skala as part of a class that also included the three 2018 Nobel Laureates in physics, Arthur Ashkin, Gerard Mourou and Donna Strickland.

SCRMC research team at the forefront of studies

Brian Walczak, D.O., UW Health, School of Medicine and Public Health received a New Investigator Recognition Award (NIRA) at the 2019 Orthopaedic Research Society Annual Meeting for his research to investigate chondrogenesis of rejuvenated mesenchymal stem cells.

From a field of over 2,000 submitted abstracts, his study, "Epigenetically reprogrammed synovial fluid-derived mesenchymal stem cells demonstrate enhanced therapeutic potential for treatment of chondral disease," was one of 15 selected internationally and one of only two involving cartilage repair. Co-authors included Hongli Jiao, Ph.D; Ming-Song Lee, M.S; and Wan-Ju Li, Ph.D., associate professor of orthopedics and rehabilitation, biomedical engineering and chair of the SCRMC Musculoskeletal Regeneration Research Group.

This was a remarkable accomplishment, says Li., "This highly competitive award recognizes young investigators and their outstanding work." "Through Brian's promising work," he adds, "we hope to make a difference for the millions of people who need relief from the pain and disability of degenerative cartilage disease. This joint disorder has become a major health concern in our society and the only option available is joint replacement with metal/plastic protheses."

With Li as his mentor, Walczak has succeeded in regenerating cartilage by injecting reprogrammed human mesenchymal stem cells (MSCs) and implanting them into guinea pig joints. This is a promising preclinical step to advancing stem cell-based treatments for osteoarthritis.

Walczak has seen his share of cartilage injuries, especially as the team physician for the UW Badger men's hockey team. His clinical focus as a UW Health doctor of orthopedics and rehabilitation is hip preservation, knee and shoulder arthroscopy, and cartilage restoration.

"We are a big cartilage transplant center here, using plugs of cartilage from donors," Walczak said in a recent SCRMC seminar, "but the grafting techniques damage cartilage and the shelf life of the grafts is not very long, plus it is a few weeks of difficult, invasive procedures."

Brian Walczak, D.O.

"Osteoarthritis is a complex, degenerative process involving the interaction of several tissues," he added. "We are working toward a minimally invasive procedure involving the cellular reprogramming of MSCs derived from fluid near the joint itself."

advancing therapies for cartilage repair

The procedure would be less invasive than a bone marrow biopsy or fat aspiration as the source of the MSCs. Once derived and then reprogrammed, the research team observed, the cells grow very well in culture, even better than cells from natural cartilage. They also grafted well into the guinea pig joints.

“We found a striking restoration of cartilage,” Walczak said.

> *“You can’t just inject stem cells directly into joints to repair cartilage, because their quality varies from patient to patient, leading to inconsistent therapeutic outcomes. One way to overcome this issue is to reprogram them. It’s complicated, but it’s necessary.”*

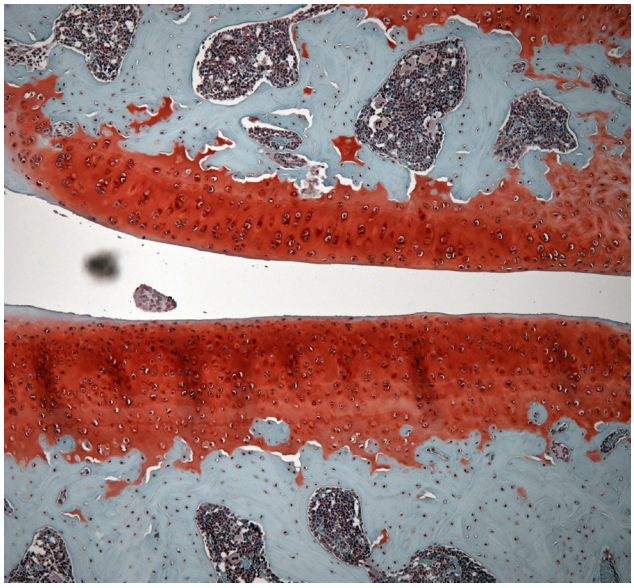
Directly injected MSCs have shown evidence of reducing pain and inflammation in both animal and human studies, but they may not be the appropriate cell type for regenerating cartilage necessary to repair actual joint damage.

“On top of that, you can’t just inject stem cells directly into joints to repair cartilage, because their quality varies from patient to patient, leading to inconsistent therapeutic outcomes,” Walczak emphasized. “One way to overcome this issue is to reprogram them. It’s complicated but it’s necessary.”

Walczak closed his talk by thanking Wan-Ju Li for his mentorship and research resources and also acknowledging Igor Slukvin, Ph.D., SCRMC faculty member and professor of pathology and laboratory medicine for his technical support.

“Wan-Ju has been a great supporter and mentor of my work,” said Walczak, who is training with Li through the UW Institute for Clinical and Translational Research. “He allows me to function as both a surgeon and a basic scientific researcher.”

The Musculoskeletal Regeneration Group members, led by Li, have accomplished other milestones in the last five years. A few of the advances include discovering how to make muscle cells from human stem cells (Masatoshi Suzuki lab, 2014), identifying a novel macrophage cell therapy for tendon repair (Peiman Hematti lab, 2017) and finding key cues to regulating bone-building cells (Wan-Ju Li lab, 2017).



Cartilage repair of an osteoarthritic guinea pig joint after injection of reprogrammed human stem cells derived from joint fluid. The repair is shown by the surface smoothness and the amount of proteoglycan (a protein abundant in cartilage) indicated by the red-orange staining intensity of Safranin O. The gray color depicts subchondral bone. The control animal without treatment showed an uneven and broken cartilage surface and lighter Safranin staining. The white space in the middle is a joint space between the femur and the tibia. (Image courtesy of the Li group.)

Our mission

The UW–Madison Stem Cell and Regenerative Medicine Center (SCRMC) operates under the School of Medicine and Public Health (SMPH) and the Office of the Vice Chancellor for Research and Graduate Education. The center provides a central point of contact, information and facilitation for campus stem cell researchers.

SCRMC faculty members collaborate across several UW–Madison schools, colleges, departments and centers, including SMPH, UW Health, College of Engineering, Wisconsin Institute for Discovery, Morgridge Institute for Research, Waisman Center, Wisconsin National Primate Research Center, School of Veterinary Medicine and many others.

The center's mission is to advance the science of stem cell biology and foster breakthroughs in regenerative medicine through faculty interactions, research support and education. To help the best minds solve the most difficult problems and move our field ahead, the SCRMC:

- Facilitates campus collaboration through scientific focus groups that meet frequently to share research progress and next steps.
- Co-funds pilot research project grants with the UW-Madison Institute for Clinical and Translational Research.
- Hosts scientific conferences and visiting professors to spur shared knowledge and collaboration.
- Provides core research services and shared equipment to researchers.
- Supports undergraduate, graduate and post-doctoral education, training and mentoring programs.
- Supports public outreach programs that inform thousands of teachers, students, families and civic groups.

Make an impact

You play a vital role in the future of stem cell research. Your investment will yield rewards that will help change the future of medicine and health care. You can choose to support:

- Basic, preclinical or clinical research in a specific area.
- Education and training for students and post-doctoral fellows.
- A general fund that gives the center maximum flexibility to take advantage of new opportunities.

Please contact Lisa Oimoen, 608-308-5328 to make a gift in support of our important work. You may also complete the enclosed gift envelope or donate on line.

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