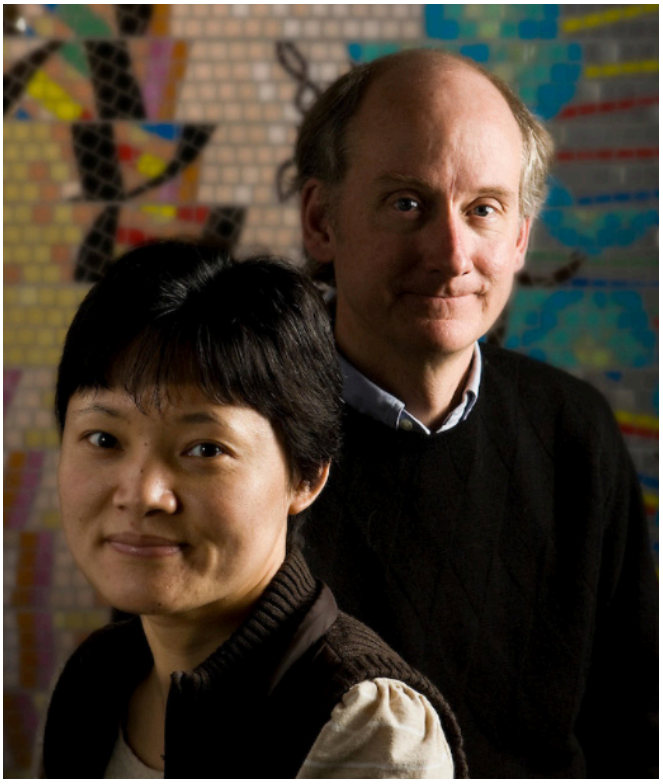
Stem Cell & Regenerative Medicine Center
UNIVERSITY OF WISCONSIN–MADISON

2017 Update



10 years of supporting vital research, education, discovery and innovation

Ten years have passed since the founding of the Stem Cell and Regenerative Medicine Center at the University of Wisconsin-Madison. It's exciting to see how much our center has grown and it's especially rewarding to see pluripotent stem cell derived therapies now moving into human patient clinical trials. We feature some of these advances in this year's SCRMC Update.

We are also proud to recognize the 10th anniversary of the successful derivation of induced pluripotent stem cells from human somatic cells, published by SCRMC faculty member James Thomson, V.M.D., Ph.D., and his lab team in *Science* on Nov. 20, 2007. Thomson continues his many research collaborations on campus and beyond as director of regenerative medicine at the Morgridge Institute for Research.

Thanks to growing collaborations within and among our SCRMC scientific focus groups and with colleagues at other universities as well as in industry, many long-envisioned stem cell therapies are now in clinical trials.

Above: James Thomson with Junying Yu, lead author on the Nov. 20, 2007 Science paper and assistant scientist at the Genome Center of Wisconsin and the Wisconsin National Primate Research Center. Yu went on to work at Cellular Dynamics International and is now chair of NuwaCell in China. (Bryce Richter image, University Communications.)

About the SCRMC

Welcome to our annual update sharing cutting-edge discoveries by our SCRMC scientists and physicians, student highlights and impacts of stem cell research in Wisconsin and beyond.

SCRMC faculty members collaborate across several UW-Madison schools, colleges, departments and centers, including the School of Medicine and Public Health, 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.

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 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.

(Sue Gilbert image)

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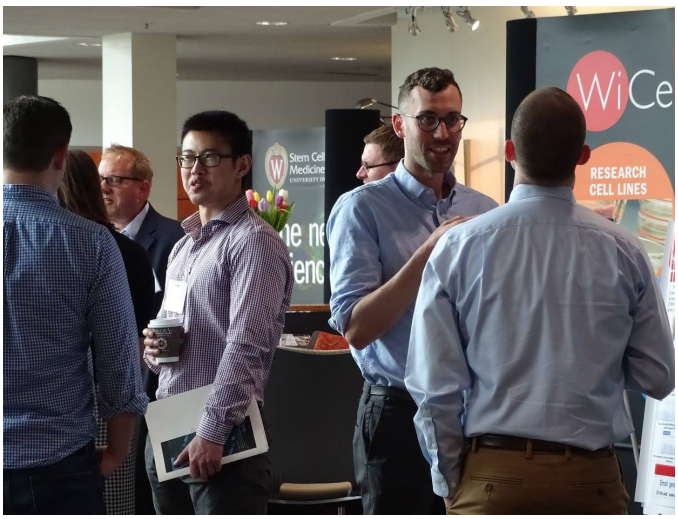
The SCRMC helps strengthen UW-Madison as the place to receive the best education, training and real world experience. We make discoveries, build partnerships, and support the next generation of scientists, clinicians and business leaders – all working together to improve our health and quality of life.



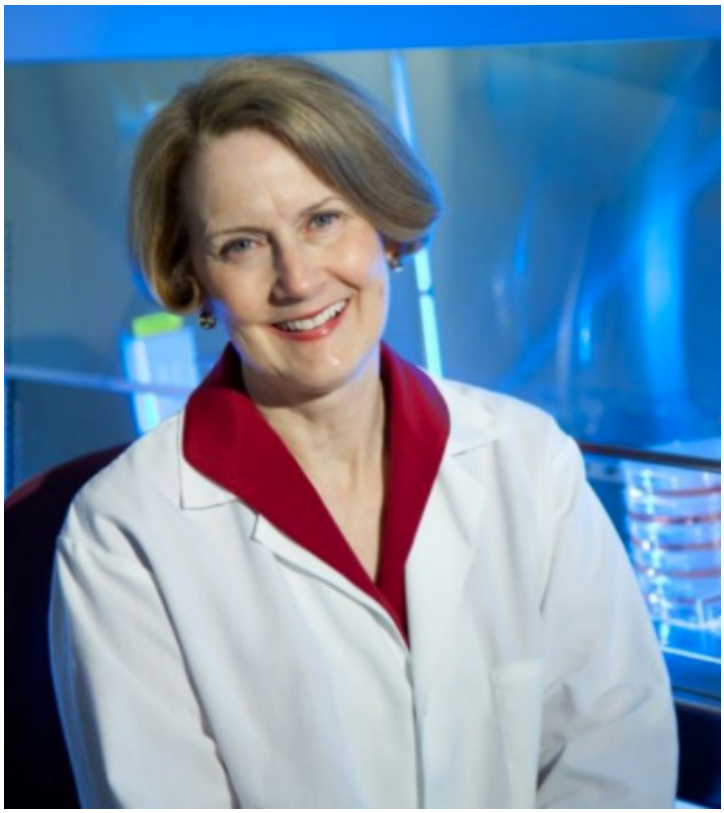
SCRMC faculty startup highlights

JangoBio is refining a stem cell-based solution for restoring the flow of hormones in aging patients. Through their "next-generation" hormonal replacement therapy, company leaders hope to help prevent diseases like Alzheimer's and diabetes, along with other aging-related issues like weight gain and fatigue. The company's CEO is Craig Atwood, Ph.D., professor of medicine and a researcher at the Wisconsin Alzheimer's Institute.

Opsis Therapeutics is a new startup of Cellular Dynamics International that is developing a pipeline of therapeutic candidates to treat retinal diseases and their associated vision loss. David Gamm, M.D., Ph.D., associate professor of ophthalmology and visual sciences, is the chief scientific officer for Opsis. Specifically, he is working on iPSC manufacturing, iPSC differentiation into retinal lineages, retinal cell biology, preclinical modeling of retinal disease, and sub-retinal surgery.

BrainXell produces and sells specialized neurons to drug researchers. Company co-founder Su-Chun Zhang, M.D., Ph.D., professor of neuroscience and neurology at the Waisman Center, was the first in the world to transform human stem cells into motor neurons. Co-founder Zhong-Wei Du, Ph.D., began working with neural stem cells in Zhang's lab about 14 years ago.

Stem Pharm Inc., a startup built on inventions related to the growth and control of stem cells, received a $290,000 grant Jan. 19 from the National Institutes of Health. The grant will support Stem Pharm's continued development of sophisticated biological materials that can efficiently manufacture stem cells for medical use. The company builds on research by founder William Murphy, Ph.D., professor of biomedical engineering.



Stratatech has advanced its regenerative skin tissue into a final-phase FDA clinical trial. Stratatech was founded by Lynn Allen-Hoffman, Ph.D., professor of pathology and laboratory medicine. The material, StrataGraft®, proved safe and effective in treating severe burns in earlier trials. It is the first severe burn therapy that has shown the potential to avoid painful skin transplants and regenerate the patient's own skin, according to Allen-Hoffmann, who is senior vice president of regenerative medicine at Mallinckrodt Pharmaceuticals, which owns Stratatech.

Lynn Allen-Hoffmann founded Stratatech and is working to transform a discovery into a biological treatment designed to speed healing of severe burns. (Photo courtesy Stratatech, a Mallinckrodt Pharmaceuticals company.)

UW treats first patient in stem cell heart trial

SMPH media relations, April 14, 2017

A research team at University of Wisconsin School of Medicine and Public Health has treated its first patient in an innovative clinical trial using stem cells for the treatment of heart failure that develops after a heart attack.

The trial is taking place at University Hospital, one of three sites nationwide currently enrolling participants. The investigational CardiAMP therapy is designed to deliver a high dose of a patient's own bone-marrow cells directly to the point of cardiac injury to potentially stimulate the body's natural healing response.

Dr. Amish Raval talks to audience members at a School of Medicine and Public Health outreach event. (Clint Thayer image)

The patient experience with the trial begins with a cell-potency screening test. Patients who qualify for therapy are scheduled for a bone-marrow aspiration. The bone marrow is then processed on-site and subsequently delivered directly to the damaged regions in a patient's heart in a minimally invasive procedure.

"Patients living with heart failure experience a variety of negative symptoms that can greatly impact their day-to-day life," said UW Health cardiologist Amish Raval, M.D., associate professor of medicine and one of the principal investigators for the trial. Raval is also chair of the SCRMC Cardiovascular Regeneration Focus Group. Members of the group meet regularly to foster interdisciplinary collaborations to translate stem cell research into new technologies for heart and vascular disease treatment and management.

"By being at the forefront of research for this debilitating condition, we look forward to studying the potential of this cell therapy to impact a patient's exercise capacity and quality of life."

The primary outcome to be measured is the change in distance during a six-minute walk 12 months after the initial baseline measurement.

Heart failure commonly occurs after a heart attack, when the heart muscle is weakened and cannot pump enough blood to meet the body's needs for blood and oxygen. About 790,000 people in the U.S. have heart attacks each year. The number of adults living with heart failure increased from about 5.7 million (2009-2012) to about 6.5 million (2011-2014), and the number of adults diagnosed with heart failure is expected to dramatically rise 46 percent by the year 2030, according to the American Heart Association (AHA).

The CardiAMP Heart Failure Trial is a phase III study of up to 260 patients at up to 40 centers nationwide. Phase III trials are conducted to measure effectiveness of the intervention, monitor side effects and gather information for future use of the procedure. Study subjects must be diagnosed with New York Heart Association (NYHA) Class II or III heart failure as a result of a previous heart attack.

Information about eligibility or enrollment in the trial is available at www.clinicaltrials.gov, or through a cardiologist. The trial is funded by Biocardia, Inc., which developed the potential therapy.

Patient's cells replicate developmental disease

Terry Devitt, May 16, 2017

The blood-brain barrier is biology's proverbial double-edged sword. An impermeable shield of endothelial cells that protects our brains from toxins and other threats that may lurk in circulating blood, the barrier can also exclude therapeutic drugs and, at times, essential biomolecules required for healthy brain development.

A case in point is the rare but severe psychomotor disease Allan-Herndon-Dudley syndrome (AHDS), a congenital condition that affects only males and starves the developing brain of thyroid hormone, resulting in cognitive impairment and atrophied muscles and motor skills. The condition is not only untreatable, but seems to be peculiar to humans, meaning scientists have been unable to study the disease and seek new treatments by modeling it in an animal like the mouse.

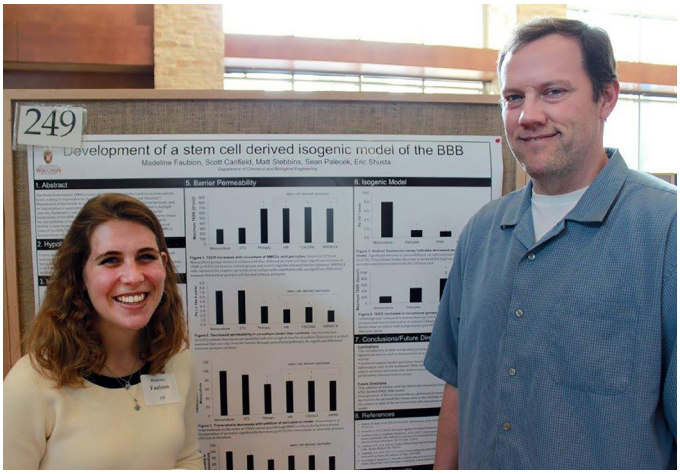
But now, a team of scientists from the University of Wisconsin-Madison and Cedars-Sinai in Los Angeles have used the cells of AHDS patients to recreate not only the disease, but a mimic of the patient's blood-brain barrier in the laboratory dish using induced pluripotent stem cell technology.

"This is the first demonstration of using a patient's cells to model a blood-brain barrier defect," explains SCRMC faculty member Eric Shusta, Ph.D., professor of chemical and biological engineering and a senior author of the new study published today (May 16, 2017) in the journal *Cell Stem Cell*. "If we had just the (compromised) neural cells available, we wouldn't have been able to identify this key characteristic of AHDS."

The new work not only establishes a laboratory model for Allan-Herndon-Dudley syndrome, but also hints at therapies that could prevent or reduce the debilitating effects of the disease, says Clive Svendsen, Ph.D., director of the Cedars-Sinai Board of Governors Regenerative Medicine Institute, a senior author of the new study and an expert on diseases of the central nervous system. The Wisconsin-Cedars-Sinai collaboration also included UW–Madison Professor of Chemical and Biological Engineering and SCRMC faculty member Sean Palecek, Ph.D., and Abraham Al-Ahmad, Ph.D., now a professor of pharmaceutical sciences at Texas Tech University.

The syndrome is caused by defects to a single gene that controls the flow of thyroid hormone to the brain. It affects the developing male brain beginning before birth and results in moderate to severe cognitive disability, impaired speech, underdeveloped muscles and involuntary movement, among other symptoms. As patients age, the condition progresses and many become confined to wheelchairs.

The research is funded by Board of Governors Regenerative Medicine Institute at Cedars-Sinai Medical Center and the NIH. *Read more.*



Eric Shusta and an undergraduate student in his lab, Madeline Faubion, present her poster on a model of the blood brain barrier at UW-Madison's Undergraduate Research Symposium April 13. (Jordana Lenon image)

Developing therapies for blindness

Acquired and inherited diseases of the retina, such as age-related macular degeneration and retinitis pigmentosa, afflict tens of millions of people worldwide.

SCRMC faculty member David Gamm, M.D., Ph.D., associate professor ophthalmology and visual sciences, is a world leader and pioneer in the differentiation and transplantation of retinal cells derived from pluripotent stem cells. He has been researching new therapies for these and other blindness disorders at UW-Madison since 1999. Gamm conducts his research at the Waisman Center and also directs the McPherson Eye Research Institute on campus.

Gamm is part of a University of Wisconsin and John Hopkins University research team awarded $12.4 million by the NIH to develop an effective way to reverse blindness. The award is part of the National Eye Institute's Audacious Goals Initiative, a targeted effort to restore vision by regenerating neurons and their connections in the eye and visual systems.

On May 2, the SCRMC and WiCell honored David Gamm, associate professor of ophthalmology & visual sciences and founder of Opsis as the 2017 Regenerative Medicine Innovator of the Year. From the left are SCRMC Co-Director Bill Murphy, SCRMC Career Enhancement Opportunities Program Chair Kris Saha, Dr. Gamm and Robert Drape, WiCell Executive Director. Thermofisher Scientific co-sponsored the event. (Sue Gilbert image)

UNIVERSITY OF WISCONSIN–MADISON
Biotechnology Center

Watch Dr. David Gamm share updates in stem cell and regenerative medicine research for treating blindness disorders.

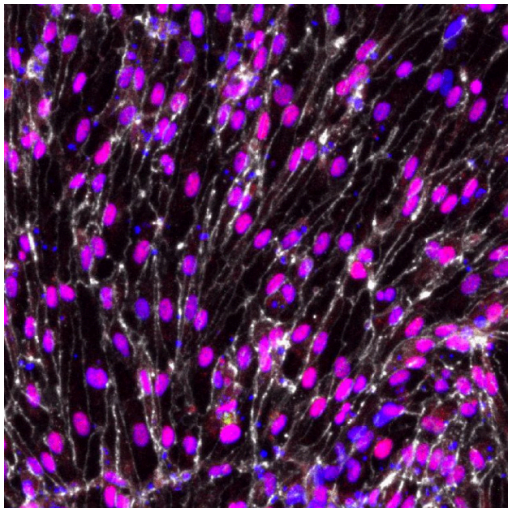
His Feb. 8, 2017 talk was part of the Wednesday Nite @ the Lab online lecture series at the Biotechnology Center. WN@TL is sponsored by the Wisconsin Alumni Assocation. The lectures also air on Wisconsin Public Television.

Bioengineered arteries are closer to reality

Brian Mattmiller, July 10, 2017

Stem cell biologists have tried unsuccessfully for years to produce cells that will give rise to functional arteries and give physicians new options to combat cardiovascular disease, the world's leading cause of death. New techniques developed at the Morgridge Institute for Research and the University of Wisconsin-Madison have produced, for the first time, functional arterial cells at both the quality and scale to be relevant for disease modeling and clinical application.

The discovery is reported in the July 10 issue of the journal *Proceedings of the National Academy of Sciences* by scientists in the lab of SCRMC faculty member James Thomson, V.M.D., Ph.D., director of regenerative biology at Morgridge and professor of cell and regenerative biology.



Arterial endothelial cells derived from human pluripotent stem cells. (Morgridge Institute for Research)

The cells contributed to new artery formation and improved survival rate of mice used in a model for myocardial infarction. Mice treated with this cell line had an 83 percent survival rate, compared to 33 percent for controls. "The cardiovascular diseases that kill people mostly affect the arteries, and no one has been able to make those kinds of cells efficiently before," says Jue Zhang, Morgridge assistant scientist and lead author. Cardiovascular disease accounts for one in every three deaths each year in the U.S., according to the American Heart Association, and claims more lives each year than all forms of cancer combined. The Thomson lab has made arterial engineering one of its top research priorities.

The research team applied two pioneering technologies to the project. First, they used single-cell RNA sequencing to identify the signaling pathways critical for arterial endothelial cell differentiation. They found about 40 genes of optimal relevance. Second, they used CRISPR-Cas9 gene editing technology that allowed them to create reporter cell lines to monitor arterial differentiation in real time.

"With this technology, you can test the function of these candidate genes and measure what percentage of cells are generating into our target arterial cells," says Zhang.

The research group developed a protocol around five key growth factors that make the strongest contributions to arterial cell development. They also identified some very common growth factors used in stem cell science, such as insulin, that surprisingly inhibit arterial endothelial cell differentiation.

"Our ultimate goal is to apply this improved cell derivation process to the formation of functional arteries that can be used in cardiovascular surgery," says Thomson. "This work provides valuable proof that we can eventually get a reliable source for functional arterial endothelial cells and make arteries that perform and behave like the real thing."

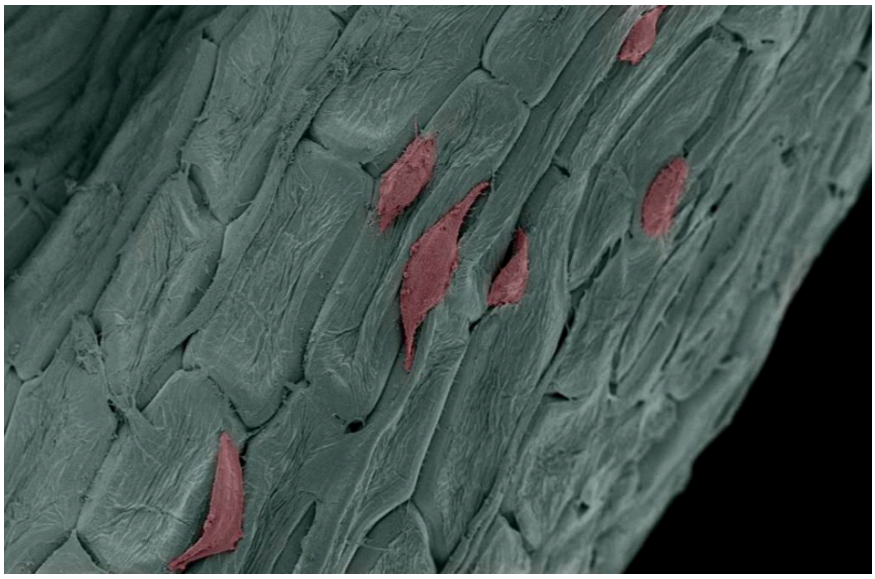
Thomson's team, along with many UW-Madison collaborators, is in the first year of a seven-year NIH project exploring the feasibility of developing artery banks suitable for use in human transplantation. *Read more.*

Nature's bounty for cell and tissue scaffolds

Terry Devitt, March 20, 2017

Borrowing from nature is an age-old theme in science. Form and function go hand-in-hand in the natural world and the structures created by plants and animals are only rarely improved on by humans.

Taking that lesson to heart, scientists at the University of Wisconsin–Madison are using the decellularized husks of plants such as parsley, vanilla and orchids to form three-dimensional scaffolds that can then be primed and seeded with human stem cells to optimize their growth in the lab dish and, ultimately, create novel biomedical implants.



Human fibroblast cells, common connective tissue cells, growing on decellularized parsley. (Gianluca Fontana image)

Writing March 20 in the journal *Advanced Healthcare Materials*, a team led by William Murphy, Ph.D., professor of biomedical engineering and SCRMC co-director, describes the use of a variety of plants to create an efficient, inexpensive and scalable technology for making tiny structures that could one day be used to repair muscle, organs and bone using stem cells.

The new technology capitalizes on the elegant, efficient structural qualities of plants: strength, rigidity, porosity, low mass and, importantly, surface area. It may help overcome the limitations of current methods such as 3-D printing and injection molding to create feedstock structures for biomedical applications.

"Plants are really special materials as they have a very high surface area to volume ratio, and their pore structure is uniquely well-designed for fluid transport," says Murphy. The UW–Madison team collaborated with Madison's Olbrich Botanical Gardens and curator John Wirth to identify plant species that could potentially be transformed into the miniature structures useful for biomedical applications. In addition to plants like parsley and orchid, Wirth and colleagues at Olbrich identified bamboo, elephant ear plants and wasabi as plants whose structural qualities may be amenable to creating scaffolds with properties and shapes useful in bioengineering. The team also collected plants such as the wetland-loving bulrush from the UW Arboretum.

The new approach to making scaffolds for tissue engineering depends on cellulose, the primary constituent of the cell walls of green plants. The team found that stripping away all of the other cells that make up the plant, and treating the leftover husks of cellulose with chemicals, entices human stem cells such as fibroblasts — common connective tissue cells generated from stem cells — to attach to and grow on the miniature structures.

The Wisconsin study was supported by the Environmental Protection Agency, the National Institutes of Health and the National Science Foundation. *Read more.*

Cues found for regulating bone building cells

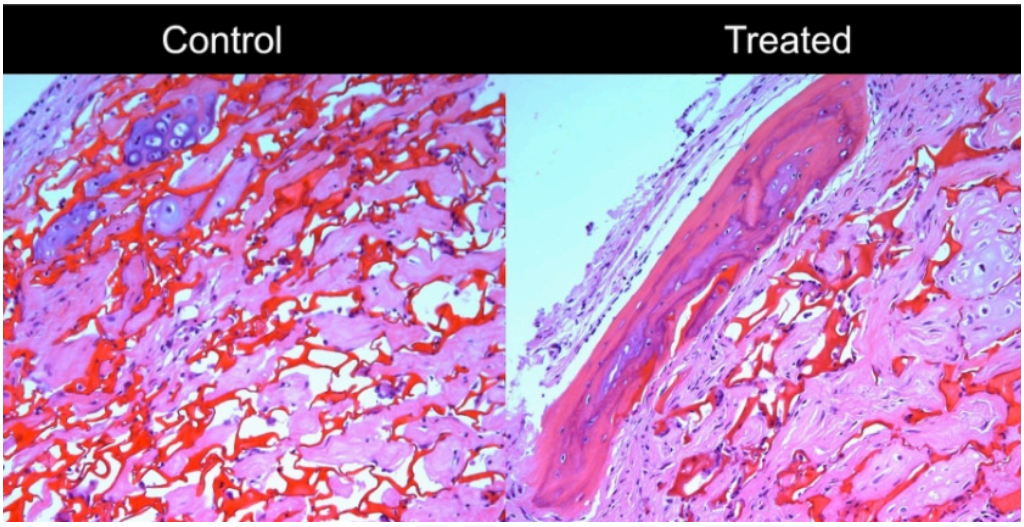
Terry Devitt, Feb. 2, 2017

The prospect of regenerating bone lost to cancer or trauma is a step closer to the clinic as University of Wisconsin–Madison scientists have identified two proteins found in bone marrow as key regulators of the master cells responsible for making new bone.

In a study published online Feb. 2 in the journal *Stem Cell Reports*, a team of UW–Madison scientists reports that the proteins govern the activity of mesenchymal stem cells — precursor cells found in marrow that make bone and cartilage. The discovery opens the door to devising implants seeded with cells that can replace bone tissue lost to disease or injury.

protein arrays to identify proteins of interest and then determined the activity of mesenchymal stem cells exposed to the proteins in culture. A goal is to better understand the bone marrow niche where mesenchymal stem cells reside in the body, to improve culture conditions for growing the cells in the lab and for therapy.

The Wisconsin researchers found that exposing mesenchymal stem cells to a combination of lipocalin-2 and prolactin in culture reduces and slows senescence, the natural process that robs cells of their power to divide and grow. Li says keeping the cells happy and primed outside the body, but reining in their power to grow and make bone tissue until after they are implanted in a patient, is key. The ability to precisely manipulate mesenchymal stem cells in the



Micrographs show the difference between untreated (left) and treated (right) bone cells in a mouse model of severe bone loss. Wisconsin researchers have identified two native protein factors important for growing mesenchymal stem cells, the master cells that make bone and cartilage, in the laboratory dish. The work could one day help make regenerating lost bone in patients a reality. (Wan-Ju Li image)

“These are pretty interesting molecules,” explains Wan-Ju Li, Ph.D., professor of orthopedics and biomedical engineering and chair of the SCRMC Musculoskeletal Regeneration Focus Group, of the bone marrow proteins lipocalin-2 and prolactin. “We found that they are critical in regulating the fate of mesenchymal stem cells.”

Li and Tsung-Lin Tsai, a UW–Madison postdoctoral researcher, scoured donated human bone marrow using high-throughput

laboratory dish and keep them poised to divide and form bone on cue helps pave the way for using cell-bearing three-dimensional matrices to reconstruct large swaths of bone lost to tumors or major trauma.

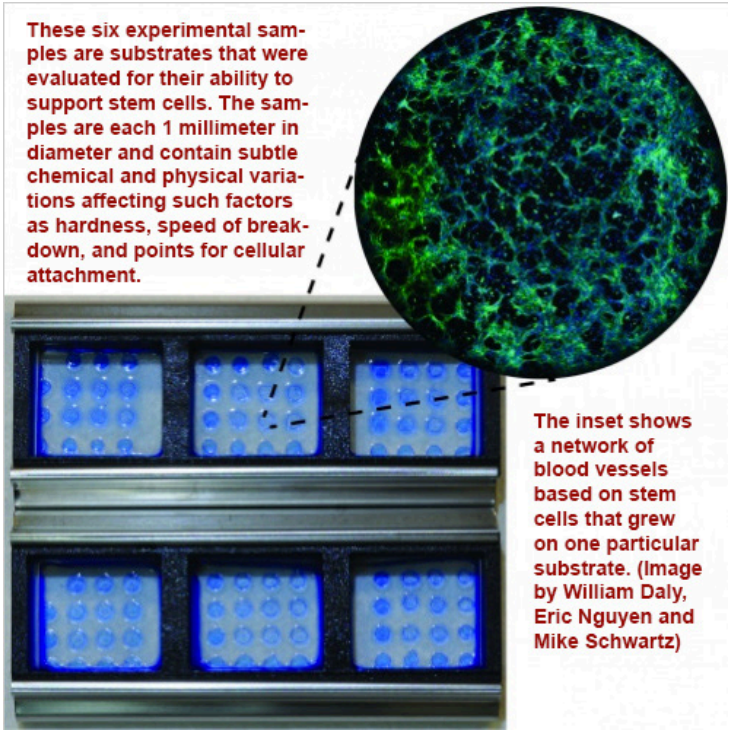
The research was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under Award Number R01 AR064803. *Read more*.

Jumping a major hurdle to growing stem cells

David Tenenbaum, July 14, 2017

Since highly versatile human pluripotent stem cells were discovered at the University of Wisconsin-Madison nearly 20 years ago, their path to the market and clinic has been slowed by a range of complications.

Now, a UW-Madison team has reported in *Nature Biomedical Engineering* that they have jumped a major hurdle on the path toward wider use of stem cells. Using an automated screening test that they devised, SCRMC Co-Director William Murphy, Ph.D., professor of biomedical engineering, and colleagues Eric Nguyen, Ph.D., and William Daly, Ph.D., have invented an all-chemical replacement for the confusing, even dangerous materials now used to grow these delicate cells.



These six experimental samples are substrates that were evaluated for their ability to support stem cells. The samples are each 1 millimeter in diameter and contain subtle chemical and physical variations affecting such factors as hardness, speed of breakdown, and points for cellular attachment.

The inset shows a network of blood vessels based on stem cells that grew on one particular substrate. (Image by William Daly, Eric Nguyen and Mike Schwartz)

"We set out to create a simple, completely synthetic material that would support stem cells without the issues of unintended effects and lack of reproducibility," Murphy says.
Stem cells respond to chemical signals that trigger their development into specialized cells in the brain, muscles and blood vessels. In the lab, researchers use a "substrate" material that anchors the cells in place and allows the necessary signaling. Matrigel, currently the most popular of these substrates, is a complex stew derived from mouse tumors. "Matrigel can be a very powerful material, as it includes more than 1,500 different proteins," says Murphy, "and these can influence cell behavior in a huge variety of ways. Matrigel has been used as a Swiss army knife for growing cells and assembling tissues, but there are substantial issues with reproducibility because it's such a complex material."

And given its biological origin, Matrigel can carry pathogens or other hazards.

In an advance that has already been granted two U.S. patents, Murphy's group has developed new substrates for raising stem cells for a wide variety of uses in regenerative medicine. Because the substrate is produced entirely from chemicals, the danger and confusion caused by the mouse proteins in existing substrates are eliminated. Another use is growing veins and arteries from stem cells, which can serve as a test-bed for evaluating drug toxicity or discovering drugs that influence blood vessel growth (such as drugs that "starve" tumors by blocking vessel growth). The widespread toxicity of drugs to developing blood vessels is one reason why so many drugs cannot be used by women who may become pregnant. Blood vessel cells derived from stem cells could also provide a new method to screen environmental chemicals for vascular toxicity, which explains why the Environmental Protection Agency has funded Murphy's work, alongside the National Institutes of Health. *Read more.*

Meet our 2017 SCRMC trainees

The SCRMC Education Committee, chaired by Kris Saha, Ph.D., assistant professor of biomedical engineering, offered 2017 SCRMC Training Awards to two graduate and two postdoctoral researchers.

Clockwise from top left, with winners pictured on the left and their SCRMC faculty mentors on the right, are:

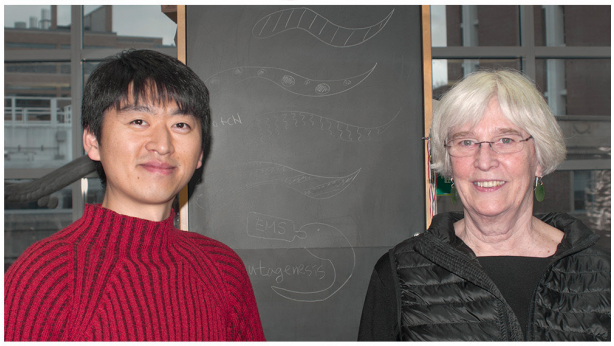
• Brandon Kim, for *iPSC derived neurovascular unit modeling of bacterial meningitis*. Mentor: Eric Shusta, Ph.D., professor of chemical and biological engineering.

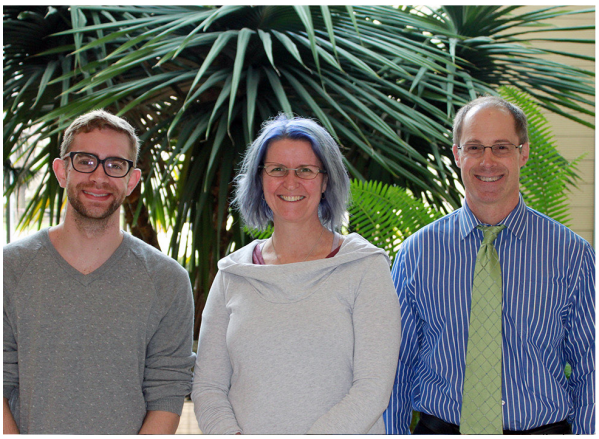
• ChangHwan Lee, for *Quantitative single-molecule analyses of Notch signaling in health and disease*. Mentor: Judith Kimble, Ph.D., professor of biochemistry.

• Zafirah Zaidan, for *Role of HP1 proteins and H3K9 methylation in pluripotency and differentiation*. Mentor: Rupa Sriharan, Ph.D., assistant professor of cell and regenerative biology and Wisconsin Institute for Discovery.

• Daniel Tremmel, for *Characterization of pancreatic extracelluar matrix (ECM) and its role in β cell differentiation, maturation, and function*. Co-mentors: Sara Sackett, Ph.D., associate scientist, surgery, and Jon Odorico, M.D., professor of surgery (transplant research and development unit).

The SCRMC Training Awards Program was established in 2008 to recognize and provide support for promising graduate students and postdoctoral fellows conducting stem cell and regenerative medicine research at the University of Wisconsin-Madison. The program provides unique, interdisciplinary training for future leaders in stem cell and regenerative medicine research. Additionally, this program aims to foster interdisciplinary collaborations among campus investigators. Each award provides training and research support for one year. *(Jordana Lenon and Laura C. Vanderploeg images)*





Our Mission

The UW-Madison Stem Cell and Regenerative Medicine Center (SCRMC) operates under the School of Medicine and Public Health 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.

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.

Our Goals

- Maintain UW-Madison as the leader in stem cell and regenerative medicine research and application.
- Foster increased SCRMC communication within campus and beyond its borders.
- Support SCRMC research: basic, translational, clinical, bioethics and public policy.
- Develop educational, training and outreach programs.
- Enhance philanthropic support.

Make a Gift

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

Your gift can support:

- Basic, preclinical or clinical research.
- Education and training for students and post-doctoral fellows.
- An unrestricted fund that gives the center maximum flexibility to take advantage of new opportunities.

Please email Lisa Oimoen or call her at 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.

For additional queries, please write, call or visit our website.

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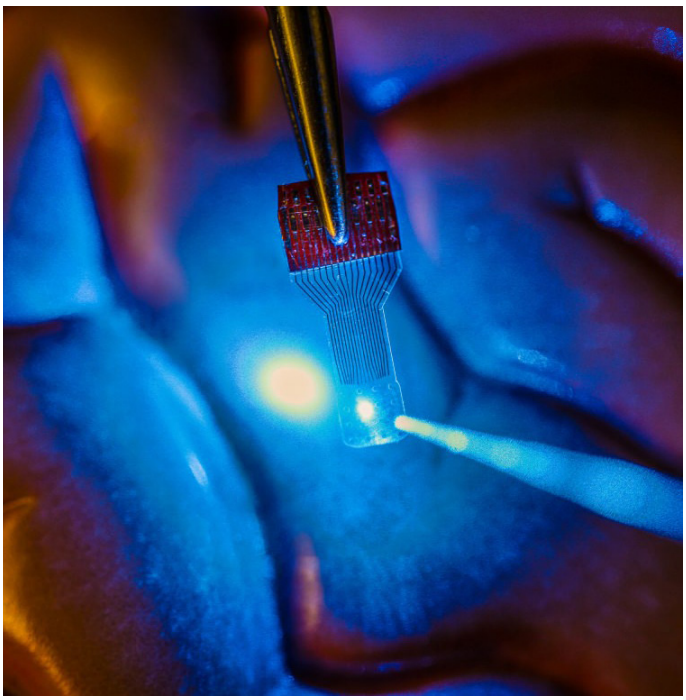

A blue light shines through a clear, implantable medical sensor onto a brain model in the lab of Justin Williams, Ph.D., professor of biomedical engineering and neurological surgery and an SCRMC faculty member. See-through sensors, which have been developed by a team of UW–Madison engineers, should help neural researchers better view brain activity. (Image courtesy Justin Williams research group)

Editing and design: Jordana Lenon

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