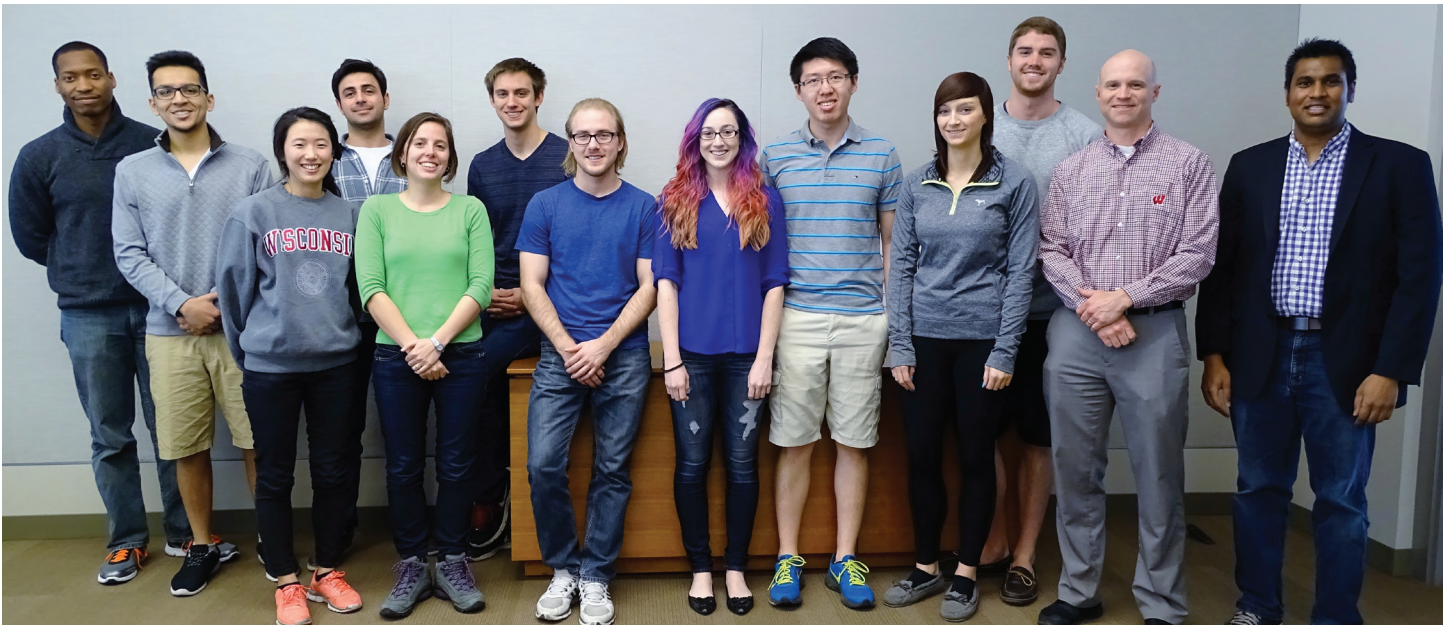




Stem Cell & Regenerative Medicine Center

UNIVERSITY OF WISCONSIN-MADISON

2016 Update



Training the next generation of stem cell industry leaders

Foundations of Innovations in Stem Cell Industries completed its first semester in May 2016. Ten students enrolled in the spring course, the first offered through the SCRMC's Career Enhancement Opportunity Program, or CEO Program for short. Pictured at the Discovery Building April 19, 2016, back row, from the left are: Scotty Cadet, Maunie Hayat, Alireza Aghayeemeibody, Dalton Hess, Timothy Abbott. Front, from the left are: Nyna Choi, Natalie Patzlaff, Brett Napiwocki, Katherine Jeffris, Steve Wang, Ashley Schwarzenstein, and [CEO professors and SCRMC members Bill Murphy and Kris Saha](#). "All 10 students were on track for internships in 2016," said Murphy. "It's all happening as we envisioned, through the SCRMC and our Education Committee partnering with industry, law firms, WARF and others. All lectures are on video and we are also interested in a multi-university course effort for expanding workforce development." (Photo by Sue Gilbert)

About the SCRMC

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

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.

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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.



Scientists, physicians, students, industry professionals and educators gather for the 11th

SCRMC fast facts

- SCRMC researchers publish approximately 500 research articles annually, including articles in *Nature*, *Science*, *Proceedings of the National Academy of Sciences*, *Cell*, and *Stem Cell Reports*.
- The SCRMC helps support more than 90 SCRMC faculty members in 40 UW departments at the University of Wisconsin-Madison, as well as more than 200 post-doctoral trainees, graduate students and undergraduate students conducting research in their labs.
- SCRMC members have been inventors on 113 issued patents since 2004.
- At least a dozen SCRMC principal investigators are working with CRISPR Cas9 and other genome editing approaches, with the goal of finding better ways to understand and treat a host of diseases and disorders.
- Wisconsin is home to more than 50 companies engaging in stem cell and regenerative medicine activities and employing more than 3,500 people.
- The SCRMC began offering an Undergraduate Certificate of Excellence in Stem Cell Sciences in Fall 2013 and 31 students have earned this certificate so far.
- Students can take the SCRMC's weekly scientific seminar series for credit and more than 399 students have done so since the series began in 2011.
- SCRMC scientists, staff and students have engaged more than 45,000 Wisconsin citizens in face-to-face and hands-on learning about stem cells and regenerative medicine since the center began its formal outreach programs in 2009.



Wisconsin Stem Cell Symposium April 13 in Fitchburg (Photo by S. Gilbert)

Brain reveals genetic secrets of development

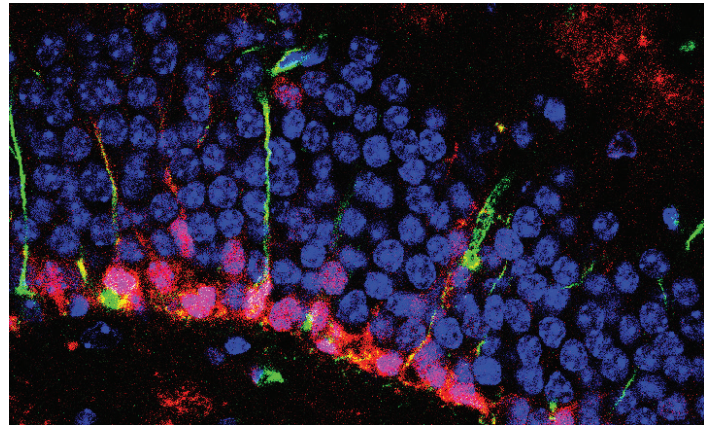
In one of the first studies to “read” the genetic activity inside individual brain cells, [SCRMC member Xinyu Zhao, Ph.D., professor of neuroscience](#), has identified the genetic machinery that causes maturation in young nerve cells. The cells under study came from the adult mouse hippocampus, a memory-related structure that is the only place in a mammal’s brain where new neurons can form throughout life. The study was published March 17, 2016 in the journal *Cerebral Cortex*.

Since newly formed neurons were discovered in the hippocampus more than 20 years ago, scientists have identified the many roles they play in learning and memory. However, mystery continues to surround the genetic controls that regulate the formation of the delicate structures

and chemicals necessary for neural communication, Zhao says.

Until the discovery of adult neurogenesis in the 1990s, scientists thought the brain essentially had to make do with the supply of neurons it acquired at birth. While trying to understand the mechanism

that regulates the formation of new neurons in adults, Zhao is also using adult neurogenesis as a model to study brain development and developmental diseases. Neurons come in many varieties and their genetic activity changes as they mature. To really understand this process, Zhao needed to know which genes are active, and when.



Xinyu Zhao has identified genetic activity in the adult hippocampus that causes stem cells to mature into fully formed neurons. Green: neural stem cells, some differentiating into neurons. Red: immature neurons. (Yu Gao image, [Waisman Center](#))



[Xinyu Zhao, Ph.D.](#)
([Waisman Center image](#))

Taking young neurons from the hippocampus of adult mice, her team isolated 84 single neurons that had differentiated from neural stem cells at least three days before — meaning they had started, but not completed, the transformation to mature neurons.

Once the data on gene activation was assembled, the researchers performed intensive analysis on the rising and falling activity of thousands of genes. The gene activation profiles of individual cells revealed that the developing neurons go through four stages. But the results also revealed hints about the origin of common neurological conditions. The most active genes during the stem cell phase overlapped significantly with genes implicated in Alzheimer’s and Parkinson’s diseases.

“It surprised us to see that genes associated with the stem cell life stage are highly represented in these neurodegenerative diseases,” says Zhao. “We do not know the significance, but it’s possible that these conditions are more related to stem cell impairment than we thought.”

Common cell transformed to master heart cell

By genetically reprogramming the most common type of cell in mammalian connective tissue, [SCRCM Co-Director Timothy Kamp, Ph.D., professor of medicine, Pratik Lalit, Ph.D.](#), and their team have generated master heart cells — primitive progenitors that form the developing heart.

Writing online Feb. 11 in the journal *Cell Stem Cell*, the scientists reported transforming mouse fibroblasts, cells found mostly in connective tissue such as skin, into primitive master heart cells known as induced cardiac progenitor cells. The technology could permit a scalable method for making an almost unlimited supply of the three major types of cells in the heart. If replicated in human cells, the feat could one day fuel drug discovery, powerful new models for heart disease and the raw material for treating diseased hearts.

The researchers found that 11 genes that play a central role in embryonic heart development could be used to reprogram the fibroblasts. They narrowed the number of essential genes to five. They also defined the conditions necessary for the transformed cells to be effectively cultured in the laboratory.

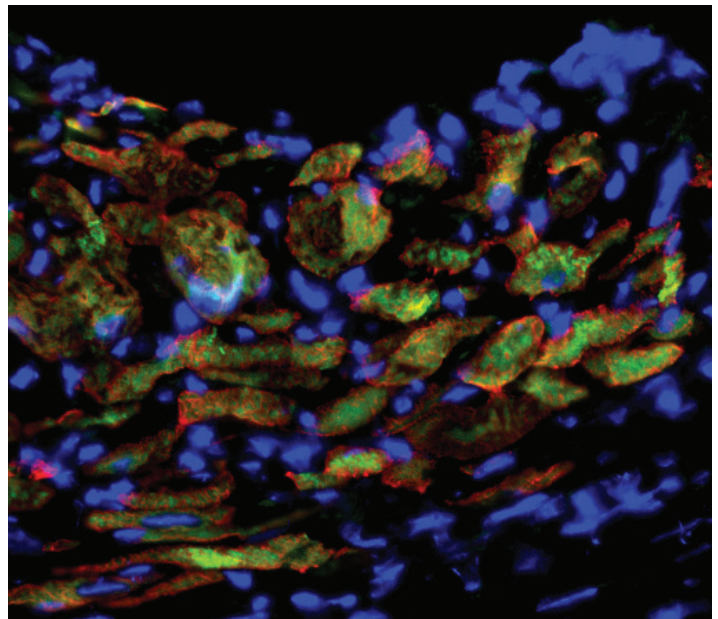
The five genes could be used to push the fibroblast cells back in developmental time to become the cardiac progenitor cells that make cardiomyocytes, smooth muscle cells and endothelial cells — the trio of workhorse cells that make up the organ. The induced cardiac progenitor cells are capable of making billions of critical heart cells with relative ease, providing ample material to study heart disease in the laboratory dish, equip high-throughput screens to test various compounds for safety and efficacy, and ultimately, to treat heart disease by replacing diseased cells with healthy ones.

A key advantage of the engineered cardiac progenitor cells is that unlike all-purpose pluripotent stem cells, which can become

any cell in the body and possibly even create tumors, the induced progenitor cells made from fibroblasts are faithful only to the cardiac lineage — a desired feature for cardiac applications. The team tested the new cells in mice by experimentally inducing heart attacks.

The implanted cells led to an uptick in survival of the mice

Injecting the engineered cells into the damaged hearts, they observed the cells migrating to the damaged part of the heart and making cardiomyocytes — the heart cells that contract to underpin the beating of the heart — as well as smooth muscle and endothelial cells, key cells that form blood vessels. The implanted cells led to an uptick in survival of the mice.



Induced cardiac progenitor cells generated new heart muscle in mice with experimentally induced heart attacks. New heart muscle cells appear as overlapping red (heart muscle protein) and green (progenitor cell protein), with cell nuclei stained blue. (Pratik Lalit image)

Cell transplants treat Parkinson's in mice

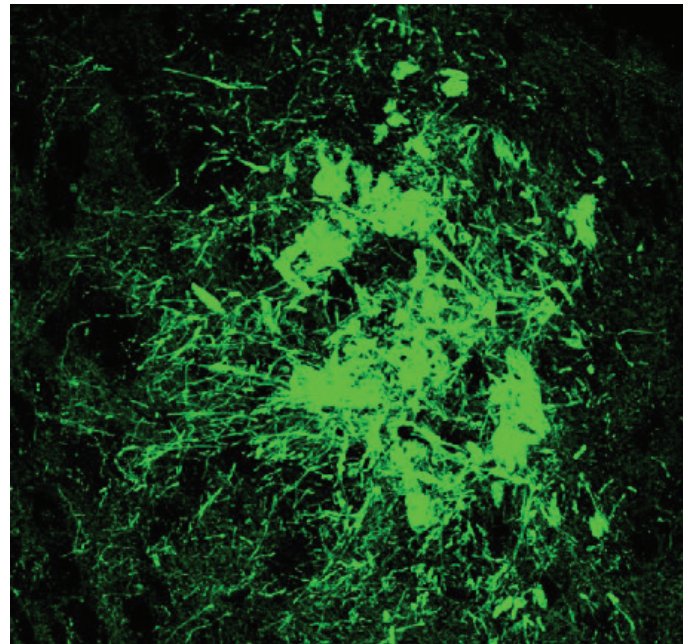
Wouldn't it be great if doctors could insert a genetic switch into a patient's cells, through designer drugs that would alter the activity of defective cells without affecting any other cells?

In a study published April 28, 2016 in the journal *Cell Stem Cell*, [Su-Chun Zhang, Ph.D., SCRMC member and professor of neuroscience at the UW–Madison Waisman Center](#), created two related cell types that may play a key role in treating Parkinson's disease. When the cells detect a new designer drug, one type ramps up production of dopamine; the other chokes it off.

Dopamine is a brain chemical essential for coordinated movement. Dopamine replacement is a standard therapy for Parkinson's disease, but it usually loses its effect with time. With the advent of stem cell technology, biomedical researchers have explored making dopamine-producing cells in the lab for transplant. While doctors have tested dopamine cell transplants, the therapy often fails when the transplanted cells make either too much or too little of the essential neurotransmitter.

Zhang and his team grew the specialized nerve cells from human embryonic stem cells, then transplanted them into mouse models of Parkinson's. Behavioral tests on the mice, designed to show when Parkinson's symptoms abated, confirmed that both the "up" and "down" switches performed as anticipated.

Zhang, who pioneered the transformation of embryonic stem cells into neural cells, sees wider application in the future. In diabetes, for example, he says that perhaps the beta cells that secrete insulin could be transplanted, and then patients could control insulin secretion with a designer drug.



Su-Chun Zhang, Ph.D., at the Waisman Center has transplanted human dopamine-producing nerve cells into mouse models of Parkinson's disease. The new cells, shown in green, responded to two separate drugs that turned them on or off as needed. (Su-Chun Zhang image)

The research advance was spurred by the new, highly precise form of "gene editing" called CRISPR Cas9.

Cell therapy was one of the most touted potential benefits of embryonic stem cells and the induced pluripotent stem cells that were later derived from adult tissue (both technologies pioneered at UW–Madison), but few applications have reached the clinic as the technology continues to be refined and made safer. Control is part of the problem, Zhang says: "If we are going to use cell therapy, we need to know what the transplanted cell will do. If its activity is not right, we may want to activate it, or we may need to slow or stop it."

The mouse study showed both abilities. Zhang anticipates that cells will someday be engineered to contain switches that work in both directions. Several major steps are already underway en route to the first clinical trial, including:

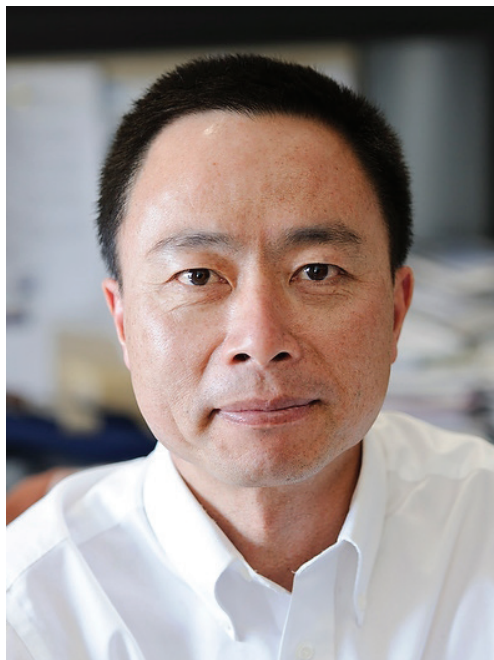
- Proving the safety of the genetically engineered stem cells, and of the drugs used for control purposes.
- Choosing transplants with maximum potential for natural, neural control of dopamine secretion.
- Ensuring that the neurons reach the brain location where dopamine is needed to control movement.
- Demonstrating success with nonhuman primate studies. “We need to prove that this is not just a mouse phenomenon,” Zhang says, “but that it really works to alleviate the symptoms of Parkinson’s disease.”

Zhang considers the discovery one the most exciting in his substantial record of scientific firsts. After the engineered cells are transplanted into the mouse brain, he says, “we can turn them on or off, up or down, using a designer drug that can only act on cells that express the designer receptor. The drug does not affect any host cells because they don’t have that specialized receptor. It’s a very clean system.”

Zhang considers the discovery one the most exciting in his substantial record of scientific firsts

The study shows, for the first time with a human stem cell transplant, that because of the new CRISPR Cas9 gene editing technology, scientists can remotely regulate the function of a transplanted cell, and in a reversible way: If they take away the drug, the original function comes back.

The research is proof of principle, using Parkinson’s disease as the model, but it may apply to many other diseases, and not just neurological diseases.



Su-Chun Zhang, Ph.D.
(Jeff Miller image)

New directions for heart disease, gene editing

Two projects by [SCRMC members](#) are among 14 highly innovative research projects chosen for first-round funding by the University of Wisconsin-Madison Office of the Vice Chancellor for Research and Graduate Education as part of the cutting edge *UW2020: WARF Discovery Initiative grants*.

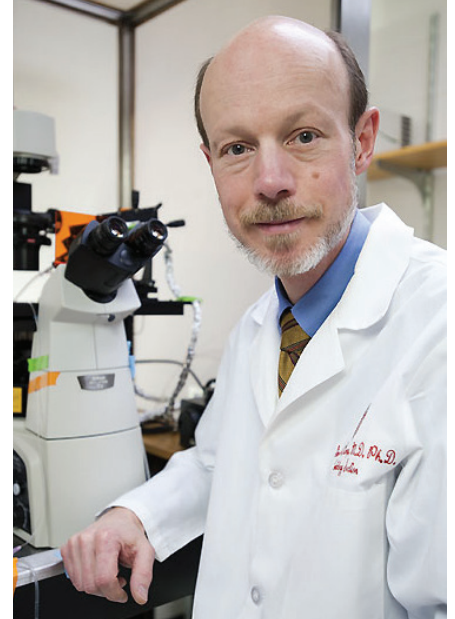
[Timothy J. Kamp, M.D., Ph.D.](#), will study the mechanisms of heart arrhythmias to develop better precision medicine-based diagnosis and treatment of lethal forms of heart disease. Cardiac arrhythmias reflect not only the electrical properties of single cardiac muscle cells, but also properties arising from the three-dimensional cardiac tissue that includes cardiac muscle cells, fibroblasts and endothelial cells.

Through their project, “[Patient-Specific Ventricular Cardiac Tissue Units for Sudden Cardiac Death Prevention](#)”, the scientists will fashion human induced pluripotent stem (iPS) cells derived from patient donors into micro-patterned structures containing all three cell types to create functional ventricular cardiac tissue units for transplant. A second goal is to develop imaging methods to allow evaluation of these new anti-arrhythmia therapies.

[Anita Bhattacharyya, Ph.D.](#), and [Su-Chun Zhang, Ph.D.](#), are co-investigators on the project, “[UW Human Stem Cell Editing Service](#).” Located in the Waisman Center, the service will provide CRISPR-Cas9 gene editing of human pluripotent stem cells (PSCs) to campus researchers, enhancing the ease and speed of many aspects of biological research across campus.

Gene editing enables the creation of genetically similar human PSC lines by correcting gene mutations in patient-donated iPSCs or by knocking a mutation into otherwise normal human PSCs. The technology will enhance the ability to understand how specific mutations cause particular diseases. In addition to using gene editing to correct or establish mutations in PSCs, new technologies enable strategies to regulate gene expression, delete genes and insert tags to allow rapid cell sorting. The new editing core will provide technical services, including generation of genome edited human stem cells lines, quality control of genome edited cells, and training for lab personnel.

Editors note: At press time, the second round of UW2020 grants were announced and include awards to three teams including SCRMC scientists Jamey Weichert (cancer vaccine research); Su-Chun Zhang and Marina Emborg (Parkinson’s neural circuits); and Rupa Sridharan and Xinyu Zhao (DNA sequencer acquisition).



[Tim Kamp, M.D., Ph.D.](#)
(Jeff Miller image)



[Anita Bhattacharyya, Ph.D.](#)
(Jerry Kalyniuk image)

Discovery holds key to blood cell expansion

By studying a genetic circuit that inhibits blood stem cell production, [Emery Bresnick, Ph.D.](#), professor of cell and regenerative biology and director of the [UW-Madison Blood Research Program](#) at the UW School of Medicine and Public Health, has identified a compound that can shut down the circuit's negative feedback loop and promote blood stem cell and progenitor cell production. Bresnick, [graduate student Xin Gao](#) and colleagues published their findings in *Stem Cell Reports* in February.

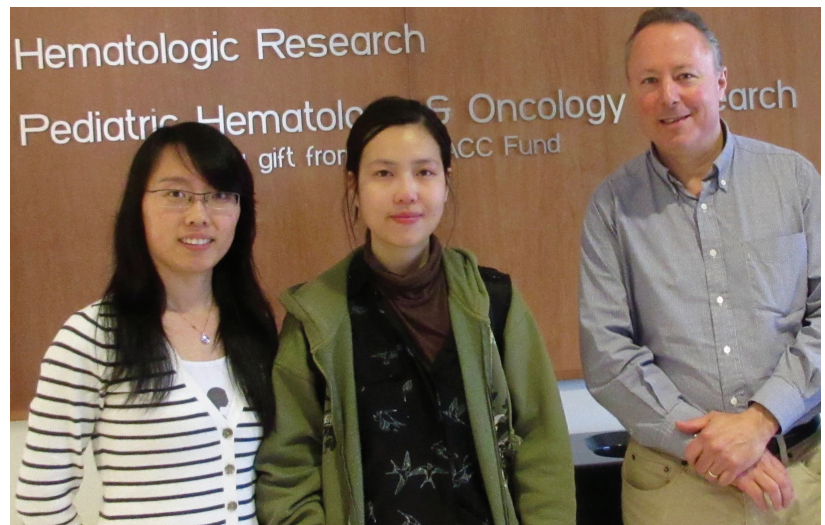
If the discovery can be applied to cord blood and transferred to the clinical setting, it could one day enable a hospital-based procedure to take a cord-blood sample and multiply its valuable stem and progenitor cells before infusion.

Cord blood, the blood from a human umbilical cord that contains hematopoietic stem and progenitor cells (blood stem cells and their offshoots), is used to treat an ever-widening range of diseases. The promise and scarcity of finding compatible cord blood transplants for patients in need had University of Wisconsin-Madison scientists searching for ways to expand these valuable cells in the lab. The Wisconsin Alumni Research Foundation recently secured a provisional patent to protect this new strategy to increase the number of blood stem cells.

Cord blood can be collected and stored at cord-blood bank facilities until needed. Most cord-blood transplants are coordinated through the National Marrow Donor Program. Once matched, the blood is prepared and delivered through an IV to its recipient. The blood-forming cells then circulate through the body and settle in the bone marrow.

More than 50,000 stem cell transplants occur annually, 2,000 of which are cord blood transplants. Roughly 70 percent of patients in need of a transplant do not have a suitable donor in their family. Unrelated-donor registries currently offer a one in 500,000 chance of finding a match. Patients seeking a bone-marrow transplant must match all six HLA types with a donor for a successful match. Cord blood matching requires only matching four of the 6 HLAs between donor and patient.

Cord blood has been used to treat many different blood disorders, immunodeficiencies, cancers and other disorders. While delivery is deceptively simple, the several months after a transplant are critical to the patient's recovery as physicians monitor the patient's health and fight infections. While it's becoming more common for adult patients to receive multiple cords to help ensure enough stem cells are transfused, the use of multiple cords may be associated with increased graft-versus-host disease, where the newly introduced cells treat the host as foreign. Thus, effective strategies to increase the number of stem cells from a single cord will have multiple benefits for patients.



From the left: Study coauthors Xin Gao, Sophie Wu and Emery Bresnick, Ph.D.

(Image courtesy Emery Bresnick)

Our students shine!

Two graduated seniors in SCRMC scientists' labs won National Institutes of Health Oxford-Cambridge Scholarships in May 2016. The scholarships are a rare honor for students pursuing doctorates in biomedical research. Only 200 individuals have taken part in the program since its founding in 2001.

[Ryan Prestil](#), of Janesville, Wisconsin, is studying at the University of Cambridge beginning in the fall of 2016. [Alex Waldman](#), of Chicago, is studying at the University of Oxford in fall 2018, following two years of medical school at Emory University.

Only 200 individuals have taken part in the program since its founding in 2001

The National Institutes of Health Oxford-Cambridge Scholars Program is an accelerated, individualized doctoral training program for outstanding science students committed to biomedical research careers. The program is based on the British system, in which students perform doctoral research without required formal courses other than those students choose to take in relationship to their own interests. Students selected for admission to the program have already developed a passion for science through engagement in summer, job-related, or undergraduate research programs.

Ryan graduated with majors in biology (neurobiology option) and mathematics, a Certificate of Excellence in Stem Cell Sciences, and the honors in research designation from the College of Agricultural and Life Sciences. For the past three years, he has worked alongside Kris Saha, assistant professor of biomedical engineering, at the Wisconsin Institute for Discovery, conducting stem cell bioengineering research and coauthoring two publications. He

received a Hilldale Undergraduate Research Fellowship in 2014 and completed a research internship at the European Molecular Biology Laboratory in Heidelberg, Germany in 2015. Ryan was president of the Student Society for Stem Cell Research on campus. He also helped found the UW-Madison Journal for Undergraduate Science and Technology.

Alex graduated in biology (neurobiology option) and Spanish, with honors in both majors. He is a member of the Phi Beta Kappa and Phi Kappa

Phi honor societies. In 2015, he received a Hilldale Undergraduate Research Fellowship to study "Age-Dependent Microglial Gene Expression Profiles in Hypoxic-Ischemic Brain Injury" with Peter Ferrazzano, associate professor of pediatrics.



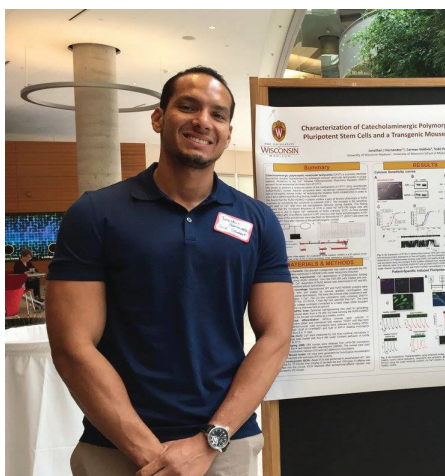
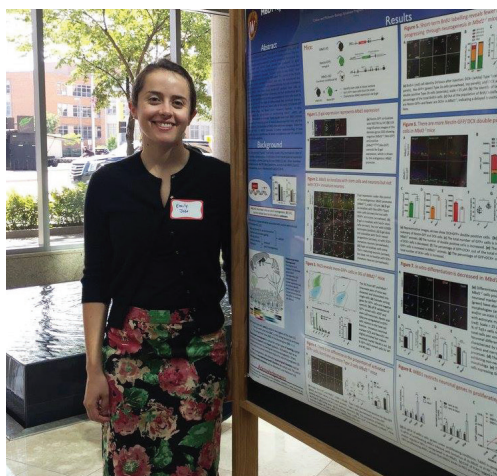
Ryan Prestil



Alex Waldman

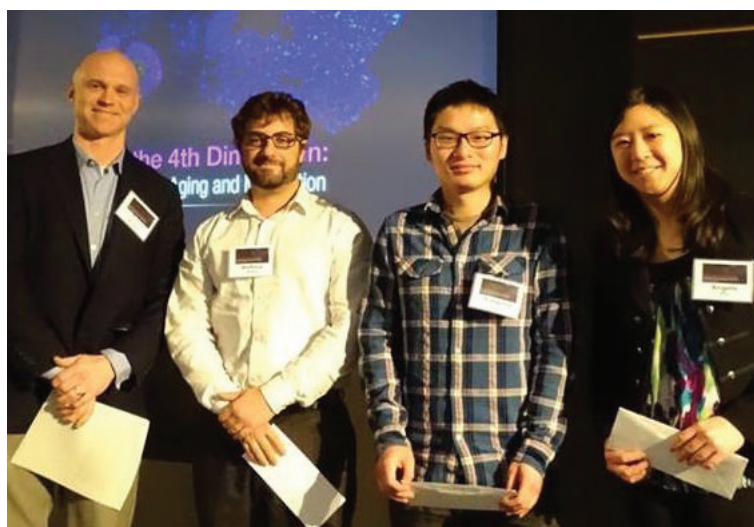
Alex worked in SCRMC member Qiang Chang's laboratory where he used CRISPR/Cas9 mediated genomic editing to model the pathophysiology of Rett Syndrome in mouse and human embryonic stem cells. He is pursuing an MD/PhD in order to fulfill his dream of becoming a physician scientist.

He also coordinated science outreach events as part of the Biocore Outreach Ambassadors student organization. *(Photos by William Graf)*



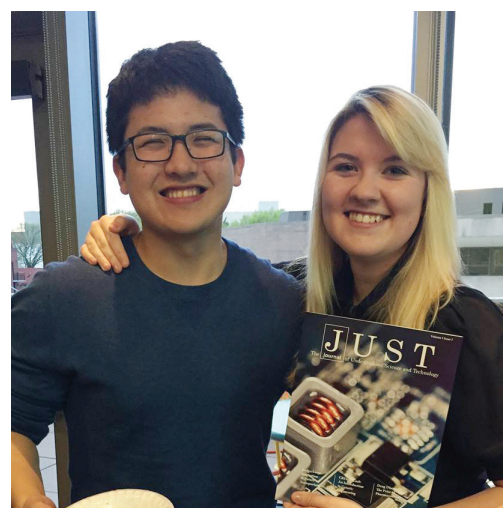
Above left: SCRCM Fall Conference poster contest winners included: [Emily Jobe](#), in Xinyu Zhao's neuroscience lab; and [Jonathan J. Hernández](#), a graduate student in the Physiology Graduate Training Program.

Above right: [Emma Doenier](#), a 2014 Wisconsin Stem Cell Roundtable fellow in Judith Kimble's biochemistry lab, was awarded a Fulbright U.S. Student Program grant in June 2016 for graduate research in Norway. Emma completed the Undergraduate Certificate of Excellence in Stem Cell Sciences, studied neurobiology and psychology, and plans to become a physician.



Center Right: Bill Murphy, SCRCM Co-Director, with this year's Wisconsin Stem Cell Symposium poster winners: 1st prize, Andrew Khalil (Biomedical Engineering, Murphy lab); 2nd prize, Xiaoping Bao (Chemical & Biological Engineering, Palecek lab); 3rd prize, Angela Xie (Biomedical Engineering, Murphy lab).

Lower Right: Posing with the first issue of the *Journal of Undergraduate Science and Technology (JUST)* in May are the journal's co-founders and editors, who are also Student Society for Stem Cell Research officers, Eddie Ruiz and Stephanie Seymour. *JUST* is written and administered by UW-Madison undergraduates with the help of faculty, staff and graduate advisors. The journal showcases and disseminates undergraduate excellence in science and technology research in strong support of the Wisconsin Idea. Seymour is in Kris Saha's lab and Ruiz has worked in the labs of Jianhua Zhang and Tim Kamp. (Photos by Sue Gilbert, Emma Doenier and Madelyn Goedland.)



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.

Support Stem Cell Research

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.

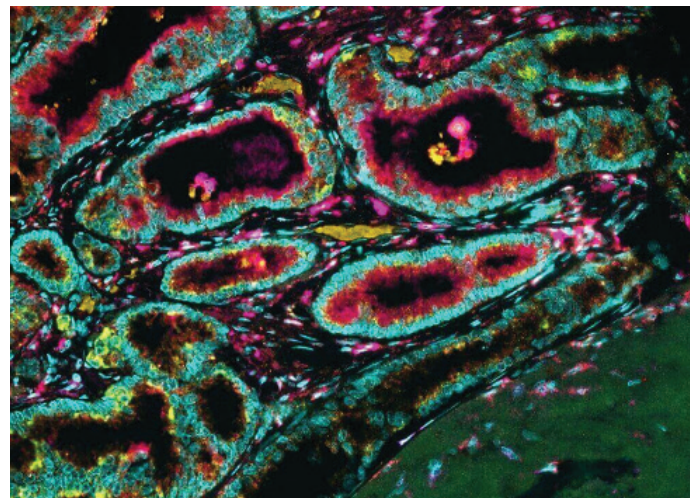
Your gift can support:

- Basic, pre-clinical 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 contact [Lisa Oimoen](mailto:lisa.oimoen@supportuw.org) at 608-308-5328 or lisa.oimoen@supportuw.org to make a gift in support of our important work. You may also complete the enclosed gift envelope, or donate on line at supportuw.org/giveto/stemcell.

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

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Karla Esbona, a postdoctoral fellow in SCRMC faculty member Patricia Keely's Cell and Regenerative Biology lab, was one of 10 winners in this year's UW-Madison Cool Science Image Contest. Above: Karla's micrograph of breast tissue from a cancer patient.

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