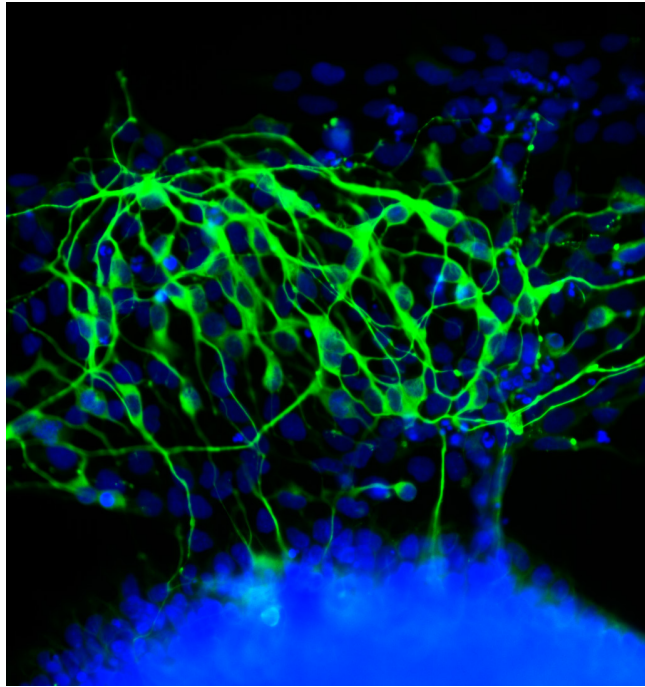




THE YEAR IN STEM CELLS

11/12



The University of Wisconsin-Madison Stem Cell and Regenerative Medicine Center (SCRMC) celebrated its five-year anniversary in 2012 with several remarkable discoveries:

- Growing blood-brain barrier cells that are important in separating circulating blood from the fluid that bathes the brain, keeping out harmful bacteria, viruses and other damaging agents
- Discovering a chemical compound that might both detect and treat malignant tumors and certain cancer stem cells
- Restoring locomotion in a mouse model of Huntington's disease
- Increasing recognition for advances in stem cell technology that have led to clinical trials for diseases and disorders of the eye, spinal cord, heart, blood and more

Encompassing 85 faculty members and scientists from more than 40 departments, the SCRMC is dedicated to moving discoveries from the laboratory into patient treatment. This year, the center's five new scientific focus groups began meeting regularly to move forward on new collaborations and discoveries. We also saw an expansion of collaborations between businesses and research in stem cell and regenerative medicine. We are pleased to share our recent groundbreaking research that helps ensure the UW-Madison remains at the forefront of this exciting and promising field. Here are some of our stories.

From the directors

This past year was very busy as you will see in this report. Yet, a great deal also happened beyond the labs and behind the scenes to keep the wheels of discovery rolling.

- One exciting change in the Stem Cell and Regenerative Medicine Center is the naming of William Murphy (Biomedical Engineering) as co-director. Bill served as associate director for over a year and has been a leader in establishing scientific focus groups in the center.
- Exciting published research on new clinical trials around the world described progress in the first human pluripotent stem cell-based therapies for disorders of the eye, spinal cord, heart, blood, and they cite the ground-breaking research from UW-Madison scientists that paved the way.
- The center's five scientific focus groups (see April 2012 highlight) began meeting regularly to work on research collaborations, plan dynamic scientific meetings, seek funding, and share and improve research methods.
- Weekly campus SCRMC laboratory meetings continued to attract large audiences at the Wisconsin Institutes for Discovery, making it easy for our diverse campus stem cell and regenerative medicine community to convene and collaborate.
- Student organizations focusing on stem cells and regenerative medicine expanded their academic and research collaborations as well as their outreach efforts: Our two active student groups on campus are the Wisconsin Stem Cell Roundtable (graduate students and post doctoral fellows) and the Student Society for Stem Cell Research (undergraduates).
- Innovative programs on the horizon in stem cell education and training include a SCRMC Certificate of Excellence in Stem Cell Science (Spring 2013), WiSCR fellowships for undergraduate research (Spring 2014), and a new "Fundamentals of Stem Cell Biology" course (Spring 2013).

We are doing all of this to advance our university's work into treating and curing the many diseases and disorders that so many of us and our loved ones continue to battle. We thank you for your continued support of the University of Wisconsin-Madison Stem Cell and Regenerative Medicine Center.

Sincerely,

Timothy J. Kamp, M.D., Ph.D.

William Murphy, Ph.D.

Co-directors, UW Stem Cell and Regenerative Medicine Center

Next page, SCRMC co-directors, left to right, William Murphy and Timothy Kamp. (Photo by Stefan Zorn.)

On the cover: "NeuroFlare" received an Honorable Mention in the UW-Madison Cool Science Image Contest in March. The photo, submitted by Samira Musah, Josue Baeza and Laura L. Kiessling, shows a colony of human embryonic stem cells differentiating into neurons. Cell nuclei are stained blue and the emerging neuronal cells express a green marker. The undifferentiated stem cells remain in tight clusters while the differentiating cells migrate out of the colonies. Basic research such as studying cell differentiation is a cornerstone of the SCRMC and the new Department of Cell and Regenerative Biology.



SEPT 11

IPS cells 99 percent similar to ES cells

In a study published September 11 in *Nature Methods*, Joshua Coon, Ph.D., associate professor of chemistry and biomolecular chemistry, reported the first full measurement of all proteins made by both types of pluripotent stem cells. The proteins of induced pluripotent and embryonic stem cells, both successfully cultured for the first time by UW-Madison stem cell pioneer James Thomson, V.M.D., Ph.D., turned out to be 99 percent similar.

Although both cell types have great potential in basic biological research and in cell- and tissue-replacement therapy, iPS cell research faces fewer ethical constraints, as it does not require patient-donated embryos. The iPS cell method instead uses patient-donated mature cells for reprogramming. These cells might also be more

useful in certain cell-replacement therapies because growing them from the patient's own cells would avoid immune rejection.

OCT 11

New partner for SCRMC

The SCRMC has partnered with the UW-Madison's newly established Department of Cell and Regenerative Biology to foster new educational and training initiatives. Faculty members in the department are committed to understanding the fundamental mechanisms by which living systems operate at cellular and molecular levels of organization. By embracing a wide range of contemporary and emerging approaches and experimental systems, investigators seek to define signaling and regulatory pathways so that they can better understand, diagnose and treat human disease.



Public outreach continues to be an important mission of the Stem Cell and Regenerative Medicine Center. This past year, SCRMC and Morgridge Outreach Experiences staff partnered with the Wisconsin Stem Cell Roundtable, a graduate student group, to provide more outreach opportunities for the public. From left, roundtable members Garrett Lee and Stefan Zorn help attendees learn how scientists work with stem cells in the lab at the September 27-29, 2012, Wisconsin Science Festival at the Wisconsin Institutes for Medical Research. (Photo by Jordana Lenon.)

Basic research is the centerpiece of the department and serves as the driving force behind teaching and training efforts. Faculty research interests are highly interdisciplinary, emphasizing molecular, cellular and systems approaches to describe biological processes in molecular terms. To maintain its excellence and stature, the department is focusing on existing strengths in four research areas: Cell and Molecular Biology, Developmental Biology, Stem Cell and Regenerative Biology, and Cardiovascular Biology.

NOV11

Transplanted neurons from ES cells successfully connect in mouse brains

Neurons forged in the lab from blank slate human embryonic stem cells and implanted into the brains of mice successfully connected with the brain's wiring to both send and receive

signals, a team of Wisconsin scientists reported in the November 21 *Proceedings of the National Academy of Sciences*. The work represents a crucial step toward deploying customized cells to repair damaged or diseased brains, the most complex human organ.

Jason P. Weick, Ph.D., staff scientist in the lab of Su-Chun Zhang, was lead author on the study. He and his colleagues transplanted the newly grown neurons into the adult mouse hippocampus, a well-studied region of the brain that plays a key role in processing memory and spatial navigation.

The capacity of the cells to integrate was observed in live tissue taken from the animals that received the cell transplants. The implanted human neurons adopted the rhythmic firing behavior of many brain cells talking to one another in unison. Such transplants could someday treat brain disorders such as Parkinson's disease and amyotrophic lateral sclerosis, more widely known as Lou Gehrig's disease.

JAN12

UW-Madison biochemist serves on national medal of science committee

UW-Madison biochemist Judith Kimble, Ph.D., was selected this month to join the President's Committee on the National Medal of Science. As a committee member, Kimble will help choose the next winners of the National Medal of Science, the nation's most prestigious science award. Established in 1959 and administered by the National Science Foundation, the award is given to about eight individuals each year who have made outstanding contributions to knowledge in the physical, biological, mathematical and engineering sciences.

Kimble is the Vilas Professor of Biochemistry at the UW-Madison and an investigator with the Howard Hughes Medical Institute. She studies the molecular regulation of animal development and has made a number of key discoveries in the field, including finding the first stem cell "niche," the micro-environment that controls stem cell maintenance.

FEB12

Stem cells used to develop safer batches of botulinum toxin

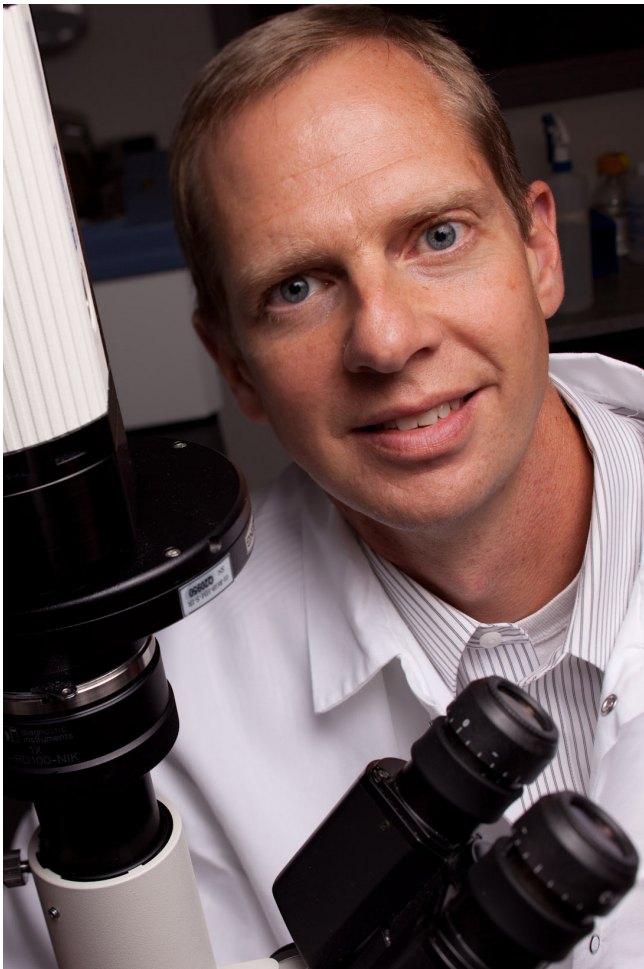
UW-Madison researchers developed an effective method using neurons grown from iPS cells to reliably and quantitatively detect botulinum neurotoxin and the antibodies that can neutralize the toxin's effects in pharmaceutical preparations. Well-known as the agent widely used to cosmetically smooth wrinkles, botulinum toxin is increasingly being used for an array of medical disorders ranging from muscle spasticity to loss of bladder control.



Biochemistry Professor Judith Kimble has been named to the President's Committee on the National Medal of Science. (Photo by Shannon McMahan.)

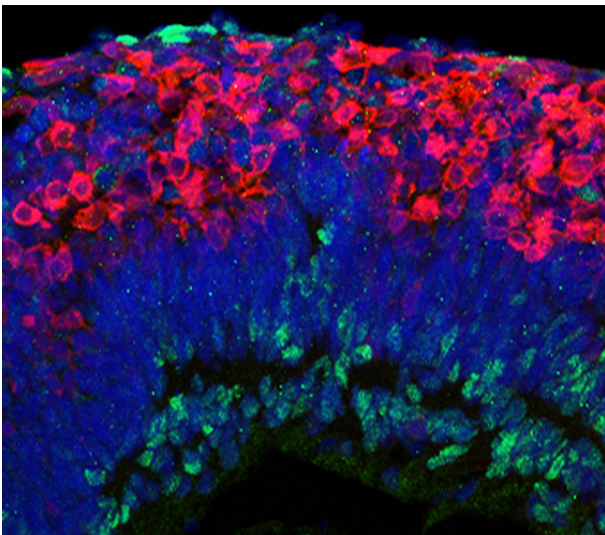
Reported February 3 in *Toxicological Sciences*, the new assay is likely to draw considerable interest from industry as a potential replacement for the mice currently used to test and control the potency of the powerful neurotoxin. Using cells provided by Madison-based Cellular Dynamics International, a company that manufactures induced pluripotent stem cells and their derivative tissue cells for use in research and industry, Professor of Bacteriology Eric A. Johnson, Ph.D., and lead researcher Sabine Pellet devised an assay that is more sensitive than the mouse assay required for quality control of pharmaceutical preparations of botulinum toxin.

The methods to produce the toxin in large quantities and to precise specifications were pioneered in the 1960s at UW-Madison by Johnson and his late mentor, Ed Schantz.



David Gamm made retinal structures using iPS cells derived from human blood. (Photo courtesy of UW Health.)

Below, retinal tissue from human iPS cells. (Image by Joe Phillips.)



MAR12

Scientists produce eye structures from human blood-derived stem cells

- For the first time, scientists have made early retina structures containing proliferating neuroretinal progenitor cells using iPS cells derived from human blood.
- In another advance, the retina structures showed the capacity to form layers of cells, just as the retina does in normal human development.
- These cells also possessed the machinery that could allow them to communicate information: Light-sensitive photoreceptor cells in the retina along the back wall of the eye, for example, produce impulses that are ultimately transmitted through the optic nerve and then to the brain, thus allowing sight.

Together, these findings suggest that it is possible to assemble human retinal cells into more complex retinal tissues, all starting from a routine patient blood sample. David Gamm, M.D., Ph.D., pediatric ophthalmologist, associate professor of ophthalmology and visual sciences, as well as senior author on the study, reported these landmark findings March 12 in *Investigative Ophthalmology & Visual Science*.

Stem cells hint at potential treatment for Huntington's disease

A special type of brain cell forged from stem cells could help restore the muscle coordination deficits that cause the uncontrollable spasms characteristic of Huntington's disease, Su-Chun Zhang, M.D., Ph.D., professor of neurology and senior author of the study, reported March 15 in the journal *Cell Stem Cell*. Currently, Huntington's disease, a debilitating congenital neurological disorder that progressively robs patients of muscle coordination and cognitive

ability, is a condition without effective treatment, a slow death sentence.

The new study revealed that locomotion could be restored in mice with a Huntington's-like condition. Zhang is a pioneering expert at making different types of brain cells from human embryonic or induced pluripotent stem cells. In this study, his group focused on using GABA neurons, cells whose degradation is responsible for disruption of a key neural circuit and loss of motor function in Huntington's patients. GABA neurons produce a key neurotransmitter, a chemical that helps underpin the communication network in the brain that coordinates movement.

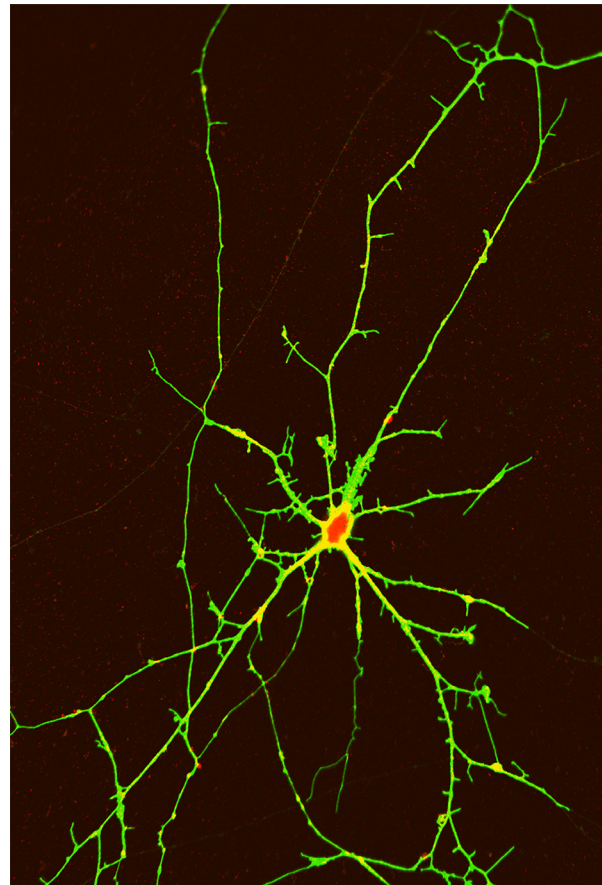
APR12

Chemical offers new hope for detecting, treating cancer cells and tumors

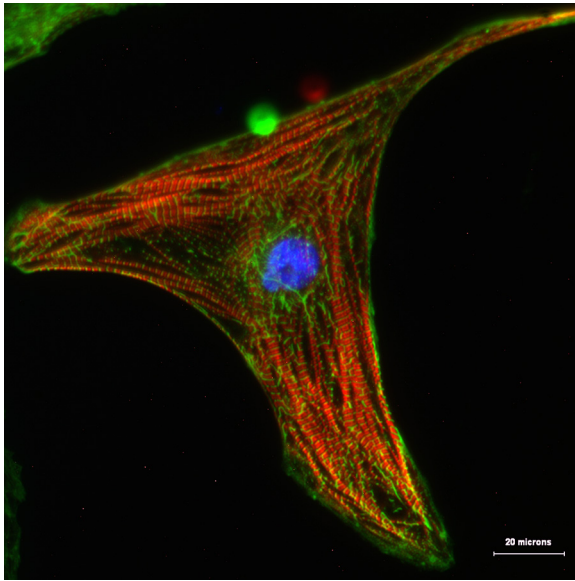
More than a decade of laboratory research at the University of Wisconsin-Madison has proven that a single chemical compound may both detect and treat malignant tumors and certain cancer stem cells.

In three posters presented at the annual meeting of the American Association for Cancer Research in Chicago, March 31-April 4, UW-Madison researchers described advances involving CLR1404. The compound, described as a "diagnostic" agent, can both image and destroy a wide range of malignant tumors and the one type of cancer stem cell examined so far.

The presentations addressed basic research in the lab of Jamey Weichert, Ph.D., associate professor of radiology and a member of the UW Carbone Cancer Center.



Above, A GABA neuron made from human stem cells in the lab of UW-Madison neuroscientist Su-Chun Zhang. GABA neurons are the brain cells whose degradation causes Huntington's disease, a condition characterized by severely degraded motor function. Zhang and his colleagues have shown that the severe motor deficits observed in a mouse model of Huntington's can be corrected by implanting the lab made cells. (Image by Su-Chun Zhang.)



Above, a single human cardiomyocyte, a work-horse muscle cell of the heart, can now be grown cheaply and abundantly in the lab, thanks to the new method devised by UW-Madison chemical and biological engineering graduate student Xiaojun Lian and his colleagues in the Palecek lab. (Photo by Xiaojun Lian.)

Scientific focus groups advance research

The seventh annual Wisconsin Stem Cell Symposium, “Neural Stem Cells - Generation and Regeneration,” convened April 11 at Madison’s BioPharmaceutical Technology Center Institute. Experts from UW-Madison and around the world discussed exciting advances in understanding how neural structures are formed, new drug targets for regeneration, and new clinical and preclinical trials using stem cell and regenerative medicine methods.

The symposium was organized by the Neural Regeneration Group, one of five SCRMC scientific focus groups established last year to stimulate new collaborations and discoveries. The other groups are Stem Cell Bioengineering, Cardiovascular Regeneration, Musculoskeletal Regeneration, and Molecular and Cellular Hematology. The Cardiovascular Regeneration focus group is organizing the 2013 Wisconsin Stem Cell Symposium.

MAY 12

New, inexpensive technique promises abundance of key heart cells

Cardiomyocytes, the workhorse cells that make up the beating heart, can now be made cheaply and abundantly in the laboratory. Writing May 28 in the *Proceedings of the National Academy of Sciences*, Sean Palecek, Ph.D., professor of chemical and biological engineering, reported a way to transform both human embryonic and induced pluripotent stem cells into the critical heart muscle cells by simple manipulation of one key developmental pathway.

The technique promises a uniform, inexpensive and far more efficient alternative to the complex bath of serum or growth factors typically used to nudge blank slate stem cells into becoming

specialized heart cells. The ability to make the key heart cells in abundance and in a precisely defined way is important because it shows the potential to make the production of large, uniform batches of cardiomyocytes routine. The cells are in great demand for research, and, increasingly, for specialized screening methods used by the pharmaceutical industry to test existing and potential drugs for toxic effects.

Chemical receptor cooperation needed to maintain normal breast cell activity

Breast-cancer researchers at UW-Madison have found that two related chemical receptors in a robust signaling pathway must work as a team to maintain normal activity in mammary stem cells. Mammary stem cells produce various kinds of breast cells and may also drive the development and growth of malignant breast tumors.

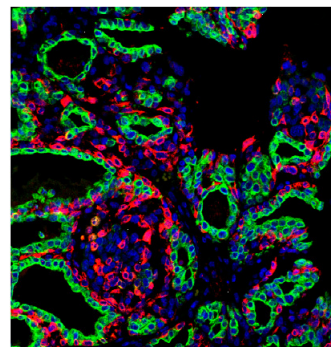
Published May 29 in the *Journal of Biological Chemistry*, the research might lead cancer drug manufacturers in new directions. Senior author Caroline Alexander, Ph.D., professor of oncology at the McArdle Laboratory for Cancer Research, detailed new information about a process known as the Wnt signaling pathway. Wnt signaling underlies numerous activities in normal development, but when problems arise along the pathway, cancer often occurs.

Scientists are working to develop the positive components of the Wnt signaling pathway for uses in regenerative medicine and to eliminate the negative cancer-causing aspects.



Above, Professor of Oncology Caroline Alexander is unlocking the mechanisms of breast cancer.

In this mouse model of basaloid human breast cancer, below, basal-like cells are red, luminal-like cells are green, and the blue is a nuclear counterstain. No stain exists to pick out stem cells, but they are scattered among the blue basal cells. Researchers are studying whether these cells interact to promote tumor growth and attempting to stop cell growth to understand how to treat these tumors. (Image courtesy of Caroline Alexander Lab.)



JUNE 12

Blood-brain barrier cells grown from stem cells could streamline drug discovery

The blood-brain barrier – the filter that governs what can and cannot come into contact with the mammalian brain – is a marvel of nature. It effectively separates circulating blood from the fluid that bathes the brain, and it keeps out bacteria, viruses and other agents that could damage it. Stroke, multiple sclerosis or other diseases and disorders, however, can disrupt the barrier. It also is often a challenge for physicians because therapeutic molecules to treat neurological disorders have a difficult time – or cannot – penetrate through it.

UW-Madison researchers have grown the cells that make up the protective barrier in a lab dish in an effort to penetrate its secrets. Writing June 24 in *Nature Biotechnology*, Eric Shusta, Ph.D., professor of chemical and biological engineering, described transforming stem cells into endothelial cells with blood-brain barrier qualities. Access to these specialized cells could streamline drug discovery for neurological disease. Pharmaceutical researchers could look at tens of

thousands of drug candidates and test whether or not they have a chance to leak into the brain.

JULY 12

Thomson lab lands \$2.2 million NIH grant

With a \$2.2 million grant from the National Institutes of Health, James Thomson, V.M.D., Ph.D., director of regenerative biology at the Morgridge Institute for Research; William Murphy, Ph.D., associate professor of biomedical engineering, and David Page, Ph.D., professor of medical informatics, will lead a team to derive and assemble the distinct cell types found in the human cerebral cortex.

The grant, one of 17 awarded nationwide on July 24, is part of a major initiative by the agency's new National Center for Advancing Translational Sciences to improve the process for predicting whether drugs will be safe in humans. In recent years, more than 30 percent of promising medications have proven to be toxic to people despite favorable results in preclinical studies using animal models. The research team intends to demonstrate how human pluripotent stem cells can be used to more effectively evaluate the safety of new drug candidates.



AUG12

Keck Foundation grants \$1 million to genome researchers

An interdisciplinary team of scientists and engineers at the University of Wisconsin-Madison has received a \$1 million grant from the W.M. Keck Foundation to fund research into creating synthetic genome “foundries.” The four faculty investigators leading the research will be SCRC member Aseem Ansari, Ph.D., professor of biochemistry and genomics; Jennifer Reed, Ph.D., professor of chemical and biological engineering; Parmesh Ramanathan, Ph.D., professor of electrical and computer engineering, and David Schwartz, Ph.D., professor of chemistry and genetics. The team hopes to improve upon the current approach to synthesizing genomes for research, which has involved copying an existing small genome via time-intensive and cost-prohibitive methods. The proposed genome foundries would consist of a suite of computational tools, novel instrumentation, hardware fabrication languages and precision-tailored small molecules.

SEPT12

New genetic mechanism found that controls blood cell development, blood vessel integrity

The protein GATA2 is known as a “master regulator” of blood cell development. When a mutation occurs in the gene that makes GATA2, serious blood diseases such as acute myeloid leukemia can result. Zooming in on the GATA2 gene, UW-Madison researchers and their collaborators at the National Institutes of Health (NIH) have discovered unexpectedly that a small DNA sequence drives this powerful master regulator. The sequence plays an essential role in controlling GATA2 production and generating self-renewing blood stem cells responsible for the earliest steps in the development of blood cells of all kinds — red cells to transport oxygen and white cells to fight infection. Emery Bresnick, Ph.D., professor of cell and regenerative biology, led the study, which appeared Sept. 10 in *The Journal of Clinical Investigation*.



Stem Cell Jeopardy, guest speakers, a poster competition and reception attracted 250 people to SCRC's Fall Conference September 21 at the Wisconsin Institutes for Discovery. The invited speakers were Deepak Srivastava, Ph.D., from the Gladstone Institute of Cardiovascular Disease, University of California, San Francisco, and UW-Madison's David Gamm, M.D., Ph.D., associate professor, RRF Emmet A. Humble Distinguished Director, McPherson Eye Research Institute, Waisman Center Stem Cell Research Program. SCRC post-doctoral fellow and graduate students organized the program. SCRC staff also unveiled the center's new, interactive website at stemcells.wisc.edu. (Photo by Stefan Zorn.)



Stem Cell & Regenerative Medicine Center

UNIVERSITY OF WISCONSIN-MADISON

Our Mission

To advance the science of stem cell biology and foster breakthroughs in regenerative medicine through faculty interactions, research support and education.

Support Stem Cell Research

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

Your gift can support several areas:

- 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.

For More Information

Visit www.stemcells.wisc.edu.

Please contact Barb McCarthy at 608-265-5891 or barb.mccarthy@supportuw.org to learn how you can support stem cell research and regenerative medicine.

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