



# Stem Cell & Regenerative Medicine Center

UNIVERSITY OF WISCONSIN-MADISON

## 2015 Update

### Mini Med School and much more!



“Mini Med School,” hosted by the School of Medicine and Public Health last September, featured research and clinical updates from SCRCMC faculty members Tim Kamp and (top, from left) Sam Gubbels, James Thomson, Sean Palecek, Bill Murphy and Amish Raval. (C. Thayer photos.)

Keeping you informed about exciting advances in stem cell and regenerative medicine research at the University of Wisconsin-Madison is one of the SCRCMC’s key missions.

Enjoy our 2015 update and please contact us to learn more!

# *The New Era of Science and Medicine*

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On the following pages, you will read about cutting edge discoveries by our SCRMC members. Our success depends on our talented and dedicated faculty, funding from the National Institutes of Health and philanthropic sources, and hard work from our collaborators and the students we educate and train.

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.

Our center 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.

## *Contact us:*

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*Drs. Tim Kamp and Bill Murphy engage in center direction, research, clinical work, and teaching and training UW students. They are also active in public outreach programs, such as the Morgridge Institute for Research's Summer Science Camp (Kamp and students above) and the UW Alumni Association/ UW-Extension Wednesday Night at the Lab (Murphy, next page).*

# *It's all about the discoveries*

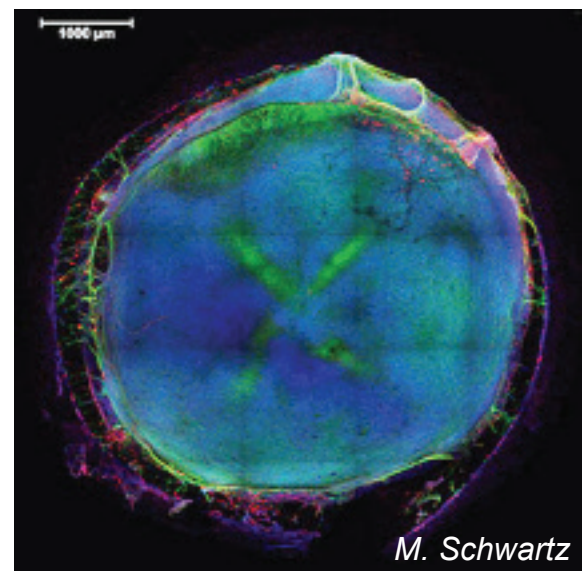
## “Tissue Chips” for Toxin and Drug Screening

Even in an era with increased emphasis on living “green,” we are constantly exposed to a wide range of toxins in everything from our air, food and water to the goods we buy. While we know the harmful effects of such substances as phthalates, VOCs, asbestos, lead and others, there are tens of thousands of toxins in our environment for which much is yet unknown.

**SCMRC Co-Director William Murphy, Ph.D.**, Harvey D. Spangler professor of biomedical engineering in the Department of Orthopedics and Rehabilitation, is leading a diverse team of UW-Madison researchers with \$6 million from the U.S. Environmental Protection Agency to develop models and screening tools to rapidly advance knowledge of the health effects of an ever-growing assortment of environmental toxins. Through the EPA Science to Achieve Results (STAR) program, the grant will create the Human Models for Analysis of Pathways (H-MAPs) Center at UW-Madison.

The team is creating “tissue chips” – clusters of interacting cells that mimic specific organs such as the developing brain (*right*). Using stem cells, miniature scaffolds and sophisticated computer programs, they’re crafting prototypes to serve as screening tools for toxins.

With connections to the College of Engineering, School of Medicine and Public Health, School of Veterinary Medicine, Morgridge Institute for Research, and Wisconsin Institute for Discovery at UW-Madison, the new center’s research team includes leading experts in stem cell biology, tissue development and microscale tissue engineering. SCMRC leaders include **James Thomson, V.M.D., Ph.D., Diplomate A.C.V.P., Randolph Ashton, Ph.D., David Beebe, Ph.D., Nader Sheibani, Ph.D.,** and **Sushmita Roy, Ph.D.**



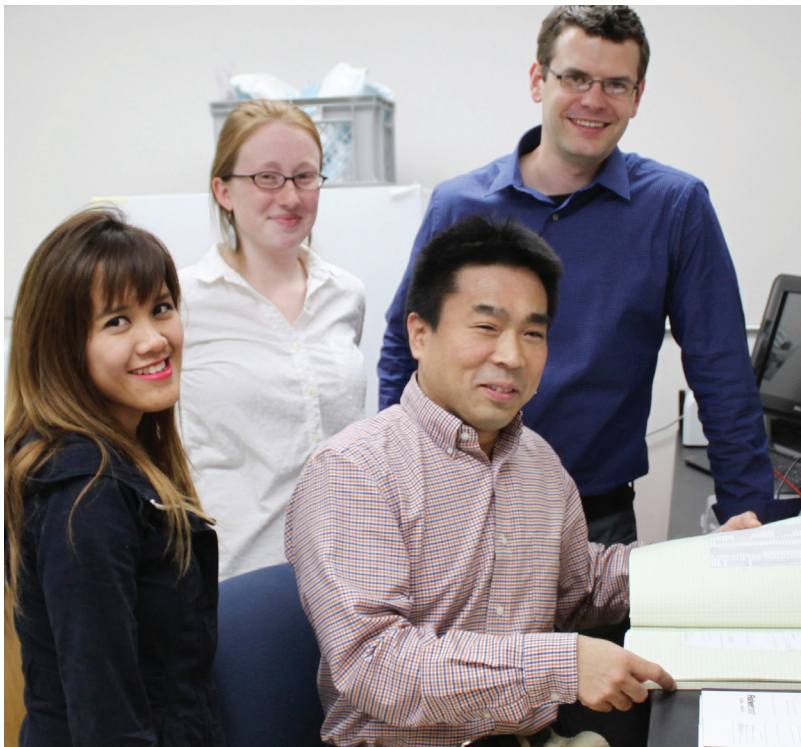
*Using microwells about a fifth the size of a dime, researchers in Dr. Bill Murphy’s Bioinspired Materials Laboratory have grown neural tissues from a combination of cell types that represent the main components of a developing brain. This image shows the entire tissue structure formed in the well, with nuclei in blue, neurons in green and glial cells in red.*



## Helping Muscles Recover from Degeneration and Injury

The neuromuscular fibers under the microscope ripple and pulse, exciting researchers who are seeking new ways to help people with damaged neuromuscular or neuroskeletal functions. Derived from pluripotent stem cells, these contracting skeletal myotubes are growing in the lab of **SCRMC member Masatoshi Suzuki, D.V.M., Ph.D.**, assistant professor of comparative biosciences in the University of Wisconsin-Madison School of Veterinary Medicine.

Suzuki wants to advance treatments for spinal cord injury, atrophy, amyotrophic lateral sclerosis (ALS), muscular dystrophy, avascular necrosis and other severe neuromuscular related disorders. With experience in studying neurons and neuroprogenitors grown from stem cells, he is now growing genetically modified stem cells and progenitors that might offer protective or regenerative properties at the base of the spinal cord. This is where the body forms new nerve-to-muscle connections that migrate to muscle sites.



Suzuki's team is genetically tweaking human pluripotent, mesenchymal and neuroprogenitor cells to infuse into the ends of rat nerves, where axons join muscles, to protect the innervations of the neuromuscular junctions. In a "prime and boost" strategy, he then treats these transplant sites with GDNF and VEGF, another growth factor, to help protect the regenerated junctions.

Finding better ways to grow different types of muscle cells is especially important as more physicians are working with scientists to launch clinical trials for neuromuscular diseases and injuries. Suzuki is working closely with Waisman Biomanufacturing to prepare cells that he hopes will be ready for such trials in the near future.

*From the left, around Suzuki seated in his lab are Saowanee Jiwlawat, D.V.M., M.S., graduate student in comparative biomedical sciences; Ivy Smit-Oistad, undergraduate research assistant, and Jonathan Van Dyke, Ph.D., postdoctoral research associate in comparative biomedical sciences. (J. Lenon photo)*

## Improving the Success of Kidney Transplants



Kidney and other organ transplants are surviving longer, but patients are not as healthy as they could be. Society has made tremendous strides in drug development to prolong graft survival, but the required life-long immunosuppressive medications have major short and long term side-effects. The current focus in transplant research is toward tolerance: graft survival without having to take 10-20 pills a day.

Working toward this goal are **SCRMC member William Burlingham, Ph.D.**, professor of surgery, **Dixon B. Kaufman, M.D.**,

**Ph.D.**, Ray D. Owen professor of surgery, and **Lynn Haynes**, distinguished researcher of transplant research and development in the School of Medicine and Public Health, along with collaborators at the Wisconsin National Primate Research Center.

A key component of transplant tolerance is the recipient's ability to accept not only the kidney, but also protective hematopoietic stem cells (white blood cells) from the donor. While there has been some clinical success establishing this situation when the donors and recipients have matched major histocompatibility complexes (MHC), the UW research team is attempting to induce acceptance with mismatched transplants. So far, so good, and the nonhuman primates in this study may just prove to be the necessary stepping stone to doing mismatched transplants in people.

In addition to the Primate Center's research and animal care experts, the UW-Madison has several experts with a world-wide reputation in their fields working on this long-term research project. They include **SCRMC member Peiman Hematti, M.D.**, associate professor of Medicine, SMPH, an expert in bone marrow transplant and stem cell research; **Lisa Forrest, V.M.D.**, professor of surgical sciences in the School of Veterinary Medicine and a tomotherapy expert, and **David O'Connor, Ph.D.**, professor of pathology and laboratory medicine, SMPH, Primate Center Research Services head, and an expert in MHC typing. (*Tomotherapy and rhesus macaque images from L. Haynes.*)

Weaning organ recipients off their anti-rejection drugs is not a trivial process. Everyone's immune system reacts differently during disease, surgery and beyond. Saving lives, and reducing the cost to patients and providers with a one-and-done transplant approach – where the patient need not take a regimen of drugs nor have to worry about a second organ transplant if the first gives out – is the “holy grail” of this work.

## Researchers Tackle Fragile X Neural Disorder

Fragile X syndrome (FXS) is the most common inherited intellectual disability and the greatest single genetic contributor to autism.

Through two revealing studies at the Waisman Center, **SCRMC member Xinyu Zhao, Ph.D.**, and **SCRMC Neural Regeneration Focus Group Chair Anita Bhattacharyya, Ph.D.**, are advancing our understanding of this disorder and exploring new drug treatments.

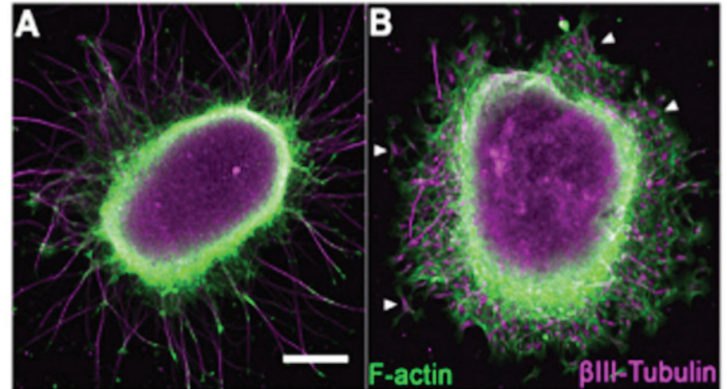
FXS affects one in 4,000 males and one in 6,000 females. It is linked to an X chromosome gene mutation and shutdown that disrupts normal production of a critical protein, FMRP.

Children with FXS often have deficits in working memory and low IQs, are more prone to anxiety, attention deficit disorder and autism, and display physical features such as a prominent jaw and forehead, and a long, narrow face.

In the first study, involving mouse genetics and published June 4 in *Cell Reports*, Zhao, SMPH professor of neuroscience, showed that two proteins might actually be involved. FMRP and another suspect protein, FXR2P, while acting through separate mechanisms in new neurons, may also work together to promote neural development.

The findings suggest that manipulating one or both proteins through drugs that foster new nerve cell development postnatally may help those with fragile X syndrome and other disorders involving malformed neurons.

A second Waisman Center FXS study involves screening drugs on neurons grown from pluripotent stem cells. This project involves three phases of research and has just been awarded additional funding from the John Merck Fund.



*Human induced pluripotent stem cells (iPSCs) were differentiated into forebrain neurons in vitro. Figure A shows normal neurons. Figure B shows neurons from iPSCs grown from FXS patients. These neurons did not mature properly and were not well connected to other neurons. (Figure by R. Nichol in the lab of Timothy Gomez, collaborating with the Bhattacharyya lab.)*

First, Bhattacharyya, Waisman Center senior scientist, with help from **SCRMC member Su-Chun Zhang, Ph.D.**, derived human iPS cells and their neural derivatives from individuals with FXS. Second, with a grant from the FRAXA Research Foundation, she and Zhao attempted to test known drugs that could reactivate the fragile X genes in these cells, but without success. In phase three, with a pilot grant from the John Merck Fund and assistance from **SCRMC member Kris Saha, Ph.D.**, she and Zhao, together with their post-doc **Meng Li, Ph.D.**, created highly sensitive “reporter cells” through gene editing, so that the FXS cells can “report” when their shut-down gene gets reactivated.

Now, with additional Merck funding, Zhao and Bhattacharyya are screening thousands of small molecule-based drugs using their reporter cells, to try and identify a drug that might cause gene reactivation. The next step will be preclinical testing in mice, with hopes of developing a breakthrough clinical therapy.

## Giving Patients More Options

When it comes to giving patients more options, **SCRMC Cardiovascular Regeneration Focus Group Chair Amish Raval, M.D., Ph.D.**, looked around his heart and vascular practice at UW Health and asked a simple, straightforward question: Which patients have the worst heart and blood vessel (vascular) related diseases?

The answer - terribly ill patients with conditions such as congestive heart failure, a recent heart attack, peripheral artery disease (PAD), or chronic angina. These patients have inspired the groundbreaking UW Options Clinic, a place where patients who have exhausted conventional medical and surgical options to treat their heart and vascular diseases can find hope in cutting-edge adult stem cell and gene therapy trials run by researchers at UW School of Medicine and Public Health.

According to Raval, an assistant professor of cardiovascular medicine with the School of Medicine and Public Health, "This is for patients who have been informed by their doctors that there are few or no treatment options available to them."

Many patients with serious heart and vascular conditions can be successfully treated at UW through the use of advanced medications or devices such as stents, heart assist devices, or, in rarer cases, heart transplants. But there are those - Raval estimates it could be as high as five percent of the patients he and his heart and vascular colleagues see in clinic - whose heart disease is simply too far advanced. In his opinion, this number is growing.

If they meet the study requirements, these patients can participate in clinical trials at the

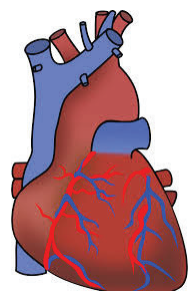
University of Wisconsin while being monitored and cared for by the nurse and research study coordinators who make up the Options Clinic staff.

In one current clinical trial, Dr. Raval is injecting stem cells into the legs of patients with severe PAD, a condition in which arteries in the legs become painfully constricted. If left untreated, PAD can lead to ulcers and amputations. Researchers are hoping that stem cells will cause the growth of new blood vessels, improving blood flow to the legs.

UW is actively involved with and recruiting patients for several other trials as well through the Options Clinic, including one that involves the use of a protein growth factor to treat advanced heart disease and another that will use adult stem cells to try to re-grow heart tissue and improve heart pump function in patients who have suffered a major heart attack.

"The truth is, the patients we're looking to reach have multiple conditions," Dr. Raval says. "It's common that a person who has peripheral artery disease could also be teetering on the brink of heart failure. This is a new way for us to approach patient focused, advanced cardiovascular disease from both a clinical treatment and scientific perspective. The Options Clinic could be a new and effective way to provide hope for these terribly ill patients."

**Patients who feel they may benefit from the Options Clinic can contact Cathlyn at [cjl@medicine.wisc.edu](mailto:cjl@medicine.wisc.edu) or (608) 262-2290.**

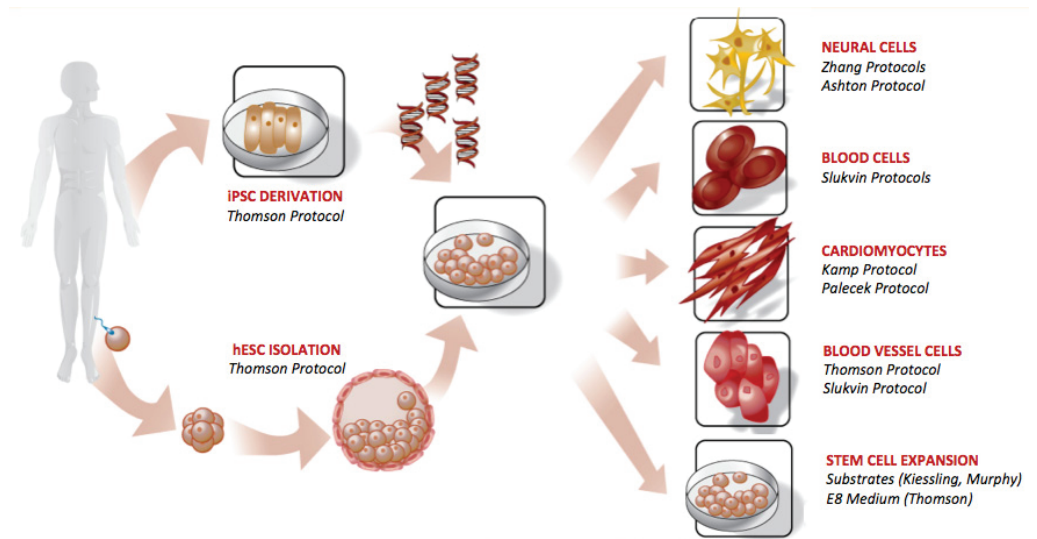


# It's all about...

## Growing Better Cells for Clinical Use

Developing a new drug takes enormous amounts of time, money and skill, but the bar is even higher for a promising stem-cell therapy. Many types of cells derived from these ultra-flexible parent cells are moving toward the market, but the very quality that makes stem cells so valuable – pluripotency – also makes them a difficult source of therapeutics. The cells we can make from stem cells

– cells for the heart, brain and liver – have amazing potential, explains **SCRMC member Derek Hei, director of Waisman Biomanufacturing**, a facility in the UW-Madison's Waisman Center, but one can also end up with the wrong type of cell if the stem cells are not fully differentiated.



Just like medicinal drugs, stem cells for clinical trials must be produced in a highly regulated environment. Waisman Biomanufacturing provides that environment – the strict regime needed to move research into developing biological products and pharmaceuticals.

One of the facility's current projects is a \$1.8 million annual contract from the National Heart, Lung, and Blood Institute to grow stem cells into specialized cells such as neurons and retinal cells for research and clinical trials. This contract supports the research of a number of SCRMC investigators at UW-Madison and beyond. For example, UW-Madison cardiac surgeon Amish Raval is using stem cells to explore how to rescue cardiac muscle cells following a heart attack.

For storing and distributing stem cells, Waisman Biomanufacturing collaborates with WiCell, a partner of the SCRMC and a nonprofit organization established in Madison in 1999, and with the Madison firm Cellular Dynamics International (CDI), a rapidly growing company begun by SCRMC faculty.

A project with CDI and Wisconsin donors aims to identify “super-donors” – people who can donate cells that would be less likely to trigger an immune attack after transplant. Cells derived from super-donor stem cells are being tested by **SCRMC member David Gamm, M.D.**, a pediatric ophthalmologist with the SMPH. Cost is a huge issue, he explains, since developing a unique line of cells for a single patient can cost \$30,000 or more. Driving down the price through growing and providing more super donor cells would be key to more mainstream, affordable health care.

All the players in the super-donor project are in-state, Hei points out. “This is coming together, and it’s all within Wisconsin. When I came here 10 years ago, this would have sounded like science fiction, but now we are on the verge of doing it.”

## Stem Cell Fast Facts

- SCRMC researchers publish approximately 500 research articles each year, including articles in Cell, Nature, Science, and Proceedings of the National Academy of Sciences. This represents output by more than 90 SCRMC faculty members in 40 UW departments, and 200 post-doctoral trainees, graduate students and undergraduate students conducting research in their labs.
- Research by SCRMC members at UW-Madison has garnered over \$40 million in NIH funding over the past year. Additional funding comes from other federal government agencies (such as the EPA), industry, and philanthropic sources.
- Wisconsin is home to more than 40 companies engaging in stem cell and regenerative medicine activities and employing over 3,500 people.
- Since 2004, SCRMC members are inventors on 95 issued patents, which have led to 28 license agreements with companies. Our members are also actively involved in starting new companies. Three of the projects being launched by the UW's Discovery-to-Product (D2P) initiative are led by SCRMC members.
- The SCRMC began offering an Undergraduate Certificate of Excellence in Stem Cell Sciences in Fall 2013, and 18 students have earned this certificate so far. Students can also take the SCRMC's weekly scientific seminar series for credit, and more than 165 students have done so since the series began in 2012.
- SCRMC scientists, staff and students have directly engaged more than 35,000 Wisconsin citizens in learning about stem cells and regenerative medicine in the past five years.



The SCRMC has cosponsored a decade of annual Wisconsin Stem Cell Symposia at the BioPharmaceutical Technology Center Institute in Fitchburg. The spring gathering brings together nearly 300 researchers, students, clinicians and business leaders in the stem cell and regenerative medicine field. *Pictured are attendees visiting vendors at the 10th meeting, focused on Engineering Limb Regeneration. (S. Gilbert photo.)*

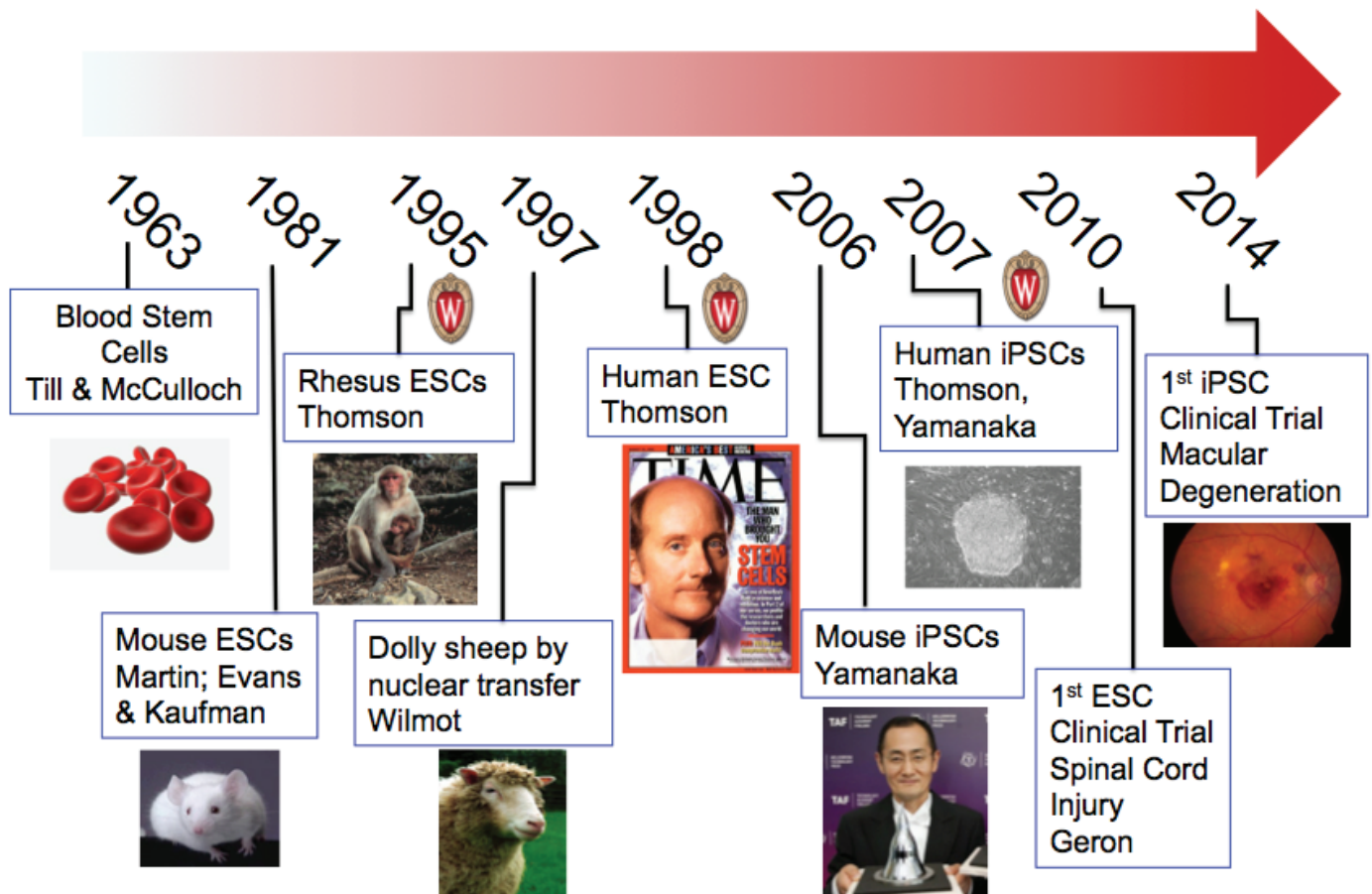
# It's all about the discoveries

## Twenty Years of Stem Cell Advances



It has been 20 years since **SCRMC member James Thomson, V.M.D., Ph.D., Diplomate A.C.V.P.**, successfully derived and cultured the world's first primate pluripotent stem cells at UW-Madison. Thomson continues to collaborate with scientists across campus and beyond to improve our understanding of stem cells and their potential. His home lab is in the Morgridge Institute for Research, where he is the director of Regenerative Biology. Thomson is also a professor in the SMPH Department of Cell and Regenerative Biology. (Thomson image courtesy of the Morgridge Institute for Research. Timeline design by W. Murphy and T. Kamp.)

### Pioneering Discoveries: Stem Cells



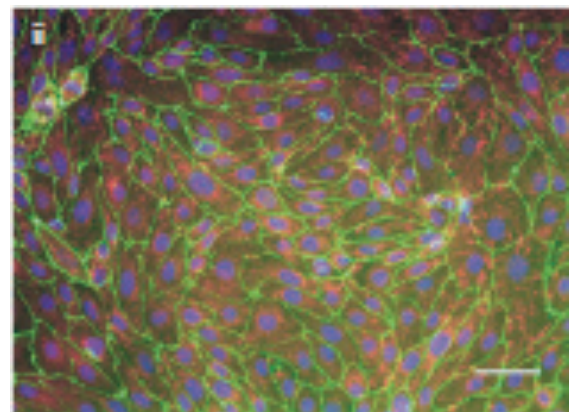
# Stem Cells: Where It Began, Where We're Going



*UW-Madison Chancellor Becky Blank, along with SCRCM scientists Bill Murphy and James Thomson, welcomed the public to the Discovery Building last September for an update co-sponsored by the SCRCM and Morgridge Institute for Research: "Stem Cells: Where It Began, Where We're Going."*

## More UW-Madison Stem Cell Breakthroughs

2001: Embryonic stem cells to neurons  
2003: ES cells to heart muscle cells  
2003: Homologous recombination in ES cells  
2005: ES cells to motor neurons  
2009: iPS cells to white blood cells  
2009: Stem cells to retina cells  
2010: Stem cell regulation in brain development  
2011: Stem cells to brain astrocytes  
2011: Stem cells to retina  
2012: Stem cells to blood-brain barrier (right, E. Shusta)  
2012: Stem cell regulation in blood development  
2012: Stem cell regulation in cancer  
2013: Genome editing in stem cells



2013: iPS cells to blood vessels  
2013: Skin cells to neural progenitors  
2013: Stem cells to bone and cartilage  
2014: Stem cells to muscle cells  
2014: Stem cells to blood  
2014: Stem cells to developing brain

## 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.

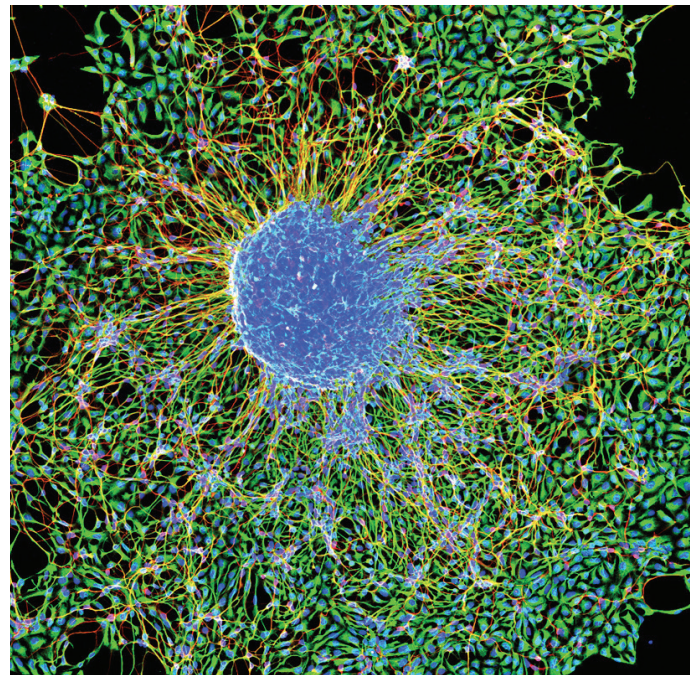
Your gift can support:

- 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 Barb McCarthy at 608-263-4545 or [barb.mccarthy@supportuw.org](mailto:barb.mccarthy@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](http://supportuw.org/giveto/stemcell).

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

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*Why Files Cool Science Image Contest Winner: marmoset embryonic stem cells forming neurons, by Scott Vermilyea, Neuroscience Training Program, School of Medicine and Public Health and neurobiology undergraduate Scott Guthrie, with SCRMC members Ted Golos and Marina Emborg, professors in the School of Medicine and Public Health and Wisconsin National Primate Research Center.*

*Editing and design: Jordana Lenon  
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