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Top of the News...

Spinal Cord Injury Research Hampered By Animal Models?

Scientists Say Difficulty Lies In Extrapolating Animal Data To Humans

[Editor's Note: Read our detailed interview with Dr. Aysha Akhtar, in which she discusses alternatives to animal-based research as well as the implications of this study for stem cell research into spinal cord injury. The interview follows below.]

Research on traumatic spinal cord injuries is hampered by a reliance on animal experiments that don't accurately predict human outcomes, according to a new study in the upcoming edition of *Reviews in the Neurosciences*.

The review was written by scientists with the Physicians Committee for Responsible Medicine.

"Despite decades of animal experiments, we still don't have a drug to cure spinal cord injury in humans," said Aysha Akhtar, M.D., M.P.H., a neurologist with PCRM and the lead author. "According to the *Journal of the American Paraplegic Society*, at least 22 agents were found to improve spinal cord injury in animals, but not one of these was helpful in humans."

The paper outlines the numerous problems with translating animal data into effective human treatments, including the many variations between laboratory-induced injuries in animals and human injuries, the difficulties in interpreting functional outcomes in animals, and the multitude of inter-species differences in physiology and anatomy.

The extrapolation problem, in general, has been widely acknowledged by scientists of many disciplines and affiliations.

According to data from the Food and Drug Administration, more than 90 percent of drugs that proved successful in animal tests are not approved for wider use after clinical trials in humans.

In February, three U.S. government agencies, including the National Institutes of Health, the Environmental Protection Agency, and

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(Continued from page 1)

the National Toxicology Program announced a major new program aimed at ending the use of animals in safety testing of new chemicals and drugs.

Because of the extrapolation challenge, some fields, such as cancer research and toxicity testing, are moving toward a greater use of alternatives.

Unfortunately, spinal cord research, a relatively newer endeavor, is not yet learning from the failure of other fields of inquiry.

As Dr. Akhtar warns, "We need to develop new, more effective research techniques."

Although scientists have just begun to develop alternatives to the use of animals in spinal cord injury research, several techniques show great promise.

Researchers at the University of Miami, for example, are collaborating on the Human Spinal Cord Injury Model Project which uses imag-

ing techniques, post-mortem analysis, and nerve conduction methods to understand human spinal cords.

Other promising directions involve computer modeling, studies on human nerve tissues, and the study of human cadavers.

At least 250,000 Americans are living with spinal cord injuries; an estimated 10,000 Americans are diagnosed each year.

Contact: http://www.pcrm.org/news/bios/aysha_akhtar.html

Q&A...

Animal-based Stem Cell Research: The Spinal Cord and Beyond: An interview with Dr. Aysha Akhbar, M.D., M.P.H.

[Dr. Akhbar is a physician who is double-board certified in both neurology and preventive medicine. She is a medical and research advisor with the Physicians Committee for Responsible Medicine (PCRM), a nationwide organization that promotes preventive medicine and addresses controversies in modern medicine, including ethical issues in research.]

Do your findings have implications for stem cell research in the spinal cord injury area?

Yes. Many of the same barriers to extrapolation from animal to human remain regardless of whether the primary experimental treatment involves stem cells, pharmaceuticals or other treatments.

The injuries induced in animals in the laboratory are still very different in multiple ways from the injuries that naturally occur in humans.

For example, unlike animals in the laboratory, humans commonly suffer from multiple systemic injuries in addition to spinal cord injury.



Aysha Akhbar

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To treat these other systemic injuries and complications, multiple drugs are given to human patients, which can affect the pharmacologic milieu and the effectiveness and safety of the experimental spinal cord treatment.

Other examples of differences in injuries between humans and animal in the laboratory include: (a) the use of laminectomy to induce injury in animals; (b) the presence of multiple stressors in the laboratory which can skew data derived from animals; and (c) the frequent presence of pre-existing spinal conditions in humans which do not occur in other animals.

Each of these differences between humans and other animals serves to impede extrapolation and will likely occur even if the experimental treatment involves stem cells.

Are there other barriers to extrapolation from animals to humans?

There are other barriers to extrapolation.

The interpretation of functional outcome in other animals, especially in mice and rats, is especially problematic.

Mice and rats and other animals can't tell us if they are experiencing improvement in sensation, for example.

At best, researchers can often only rely on a crude interpretation of their behavior, which is very unreliable.

In addition, the anatomical and physiological differences between humans and other animals are very problematic when assessing the effectiveness of stem cells designed to promote nerve growth and regeneration.

Parts of the human spinal white matter alone are equivalent in size to the diameter of the entire rat spinal cord and the human spinal cord is four times longer than the entire rat central nervous system, including brain and spinal cord.

Therefore, a much lesser amount of nerve regeneration is required to restore function in a rodent or other animal in comparison to a human.

The spinal circulatory system, metabolic and other processes that differ between humans and animals can also affect how well stem cells

take hold and function within the site of injury.

The circulatory system is crucial to maintaining healthy stem cells; differences in the systemic and local spinal circulatory system between humans and other animals will impede interpretation of results in animals.

Should stem cell scientists working on SCI be looking for other research techniques than murine-based experiments, for example?

Absolutely.

The size difference alone between humans and mice is a major problem in nerve regeneration techniques as elaborated above.

Also, response to injury within the spinal cord differs significantly between mice and humans.

In mice, a connective tissue matrix is formed, which helps facilitate repair in the spinal cord.

I suspect the presence of this matrix in mice will affect the effectiveness of stem cells.

Humans show minimal connective tissue matrix formation.

Also, in contrast to what occurs in humans, there is minimal formation of a central cavity in the spinal cord in mice.

The significantly larger spinal cord cavity in humans serves as a barrier to nerve growth and injury repair.

Thus mice have features in their spinal cord that facilitate repair and recovery after injury and any interpretation of stem cell experimental results in mice must be taken with extreme caution.

Mice may be more likely to show improvement after stem cell treatment than humans.

Another major problem with using mice and any other animal involves the problem with interpreting their behavior.

It has been well speculated that treatments intended to promote nerve regeneration can potentially cause a serious adverse outcome: they might actually cause erroneous nerve sprouting and connections that lead to significant pain and

(Continued on page 4)

dysfunction in patients.

It is extremely difficult to know if this unwanted effect is occurring in animals because many animals, especially rodents, are quite stoic and it is hard to often know if they are in pain.

We can't rely on the animal tests to know if this unwanted outcome is a real threat to humans who might receive stem cell treatments.

Better human-relevant tests need to be created.

Do you know of any researchers who are already using different research techniques?

Unfortunately, I know of no researcher who does not use animals to study stem cell therapies for spinal cord injuries.

There may be many out there – I am just not aware of them.

The problems elaborated above should illustrate why, even if there are some researchers using non-animal method for stem cell research, there needs to be a more compete shift away from using animals throughout the spinal cord injury research field.

A more human-based approach is truly needed to help patients with spinal cord injury.

What are some of the other human-based research techniques?

There are other human-based techniques that have been created for the study of other types of treatments for spinal cord injury.

These include in vitro human nerve cell and tissue cultures, in which cells can be individually or collectively injured and then treatments studied.

These models provide the opportunity to define mechanisms and intracellular signaling pathways associated with spinal cord injury and treatment.

There are also in silico models of neuronal injury and repair.

I do not know if these models are being used specifically for the study of stem cell treatments.

Heart Disease

Reprogrammed Skin Cells Create Heart And Blood Cells In Mouse Study

But Clinical Trials Are Many Years Away



Human Heart

Stem cell researchers grew functioning cardiac cells using mouse skin cells that had been reprogrammed into cells with the same unlimited properties as embryonic stem cells. The finding by researchers at the University of California at Los Angeles (UCLA) is the first to show that induced pluripotent stem cells or iPS cells, which don't involve the use of embryos or eggs, can be differentiated into the three types of cardiovascular cells needed to repair the heart and blood vessels.

The discovery could one day lead to clinical trials of new treatments for people who suffer heart attacks, have atherosclerosis or are in heart failure, said Dr. Robb MacLellan, a researcher at the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research and senior author of the study.

But, Dr. MacLellan told *Stem Cell Research News*, that "one day" probably is probably several years away, because of the need for more basic research.

Researchers also were able to differentiate the iPS cells into several types of blood cells, which may one day aid in treating blood diseases and in bone marrow transplantation.

"I believe iPS cells address many of the shortcomings of human embryonic stem cells and are the future of regenerative medicine," said MacLellan, an associate professor of cardiology and physiology. "I'm hoping that these scientific

(Continued on page 5)

findings are the first step towards one day developing new therapies that I can offer my patients. There are still many limitations with using iPS cells in clinical studies that we must overcome, but there are scientists in labs across the country working to address these issues right now.”

Last June, UCLA stem cell researchers were among several scientific teams that were the first to reprogram mouse skin cells into cells resembling embryonic stem cells, which have the ability to become every cell type found in the body.

MacLellan and his team used UCLA’s iPS cells in their study.

Although iPS cells are believed to be very similar to embryonic stem cells, further study needs to be done to confirm their differentiation potential.

MacLellan’s study proved that iPS cells can be induced into becoming cardiovascular cells, an important step in the confirmation process.

“Theoretically, iPS cells are able to differentiate into 220 different cells types,” said Dr. Miodrag Stojkovic, co-editor of *Stem Cells*. “For the first time, scientists from UCLA were able to induce the differentiation of mouse iPS cells into functional heart cells.”

In MacLellan’s study, the iPS cells were cultured on a protein matrix known to direct embryonic stem cells into differentiating into cardiovascular progenitor cells, immature heart cells that can give rise to mature cardiac cells that perform different functions.

The progenitor cells were then isolated from the other iPS cells that did not differentiate using a protein marker called KDR, a growth factor receptor expressed on the surface of the progenitor cells.

Once isolated, the cardiovascular progenitor cells were coaxed into becoming cardiomyocytes, or mature heart muscle cells that control heartbeat, endothelial cells, which form rudimentary blood vessels, and vascular smooth muscle



Robb MacLellan

cells, the specialized cells that line blood vessel walls.

Once mature, the cardiomyocytes beat in the Petri dish.

Studies are under way now at UCLA to determine if human iPS cells behave the same way as the mouse cells behave.

If they do, the time may come when a person could use their own skin cells to create individualized iPS cell lines to provide cells for cardiac repair and regeneration, MacLellan said.

It is vital to be able to grow and isolate progenitor, or partially differentiated, cells that can create the three types of cardiac cells for potential clinical use.

When embryonic stem cells are injected directly into the heart in animal models, they create tumors because the cells differentiate not only into cardiac cells but into other cells found in the human body as well.

Likewise, using embryonic stem cells garnered from other sources than the patient could result in rejection of the injected cells.

The use of iPS cells may solve those problems.

If the iPS cells come from the patient, rejection should not be an issue.

Additionally, the use of cells that are already partially transformed into specific cardiac cell types may prevent tumor growth.

The use of iPS cells also sidesteps the controversy some associate with deriving pluripotent stem cells from embryos or eggs, MacLellan said.

“Our hope is that, based on this work in mice, we can show that similar cardiovascular progenitor cells can be found in human iPS (hiPS) cells and, using a similar strategy, that we can isolate the progenitor cells and differentiate them into the cell types found in the human heart,” MacLellan said.

In fact, Dr. MacLellan, told us, “We are currently studying hiPS cells and looking for a similar progenitor.”

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Mouse Cells Don't Necessarily Predict Human Outcomes

A new study by the Physicians Committee for Responsible Medicine (*see front page article and accompanying interview in this issue*) concluded: "Research on traumatic spinal cord injuries is hampered by a reliance on animal experiments that don't accurately predict human outcomes..."

We asked Dr. MacLellan whether that spinal cord-related analysis might relate to cardiac research in animals.

Or is there a high degree of confidence that what is learned from murine cardiac studies, for example, will translate to human cardiac research?

Dr. MacLellan acknowledged the problems with mouse cells, and indicated that that was at least one of the reasons why it is important to search for human iPS cells.

"Mouse and human development have many similarities," he told us. "Thus I suspect it likely we will be able to identify a similar progenitor in hiPS."

"However," he added, "translating therapies from mouse/rat models to humans has been problematic as evidenced by the inconsistent response of cell therapy in humans. Definitely, this is the type of therapy that you would want to test in larger animal models and do long-term follow-up."

Clinical Trials Far Off

We were intrigued by Dr. MacLellan's statement that "The discovery could one day lead to clinical trials of new treatments for people who suffer heart attacks..."

What might does "one day" mean?

Dr. MacLellan essentially said, Don't hold your breath.

He said the basic research on iPS cells will take awhile before it leads to clinical trials.

But it depends on something very important.

"Realistically [the basic research could take] six to 10 years," Dr. MacLellan told *Stem*

Cell Research News. "But that will be dependent on developing new ways to derive iPS cells that do not require retroviruses. If this proceeds rapidly, it may be sooner."

The study, which brought together stem cell and cardiology researchers at UCLA, appeared online May 1 in the journal *Stem Cells*.

The article can be accessed at www.stemcells.com/papbyrecent.dtl.

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Stem Cells Found For The First Time In The Pituitary Gland

Scientists Are Just Starting To Figure Out What Their Role Might Be

Scientists have for the first time identified stem cells that allow the pituitary glands of mice to grow even after birth.

But they are not typical stem cells, and very little is known yet about what role the cells play in the pituitary's job as the master gland of the endocrine system.

Which makes it impossible to tell whether they might someday play a part in treating stress or mood disorders.

All that can really be said at this point is that the results suggest a novel way that the hormone-secreting gland may adapt, even in adolescents and adults, to traumatic stress or to normal life changes like pregnancy.

The scientists do know that, in contrast to most adult stem cells, these cells are distinct from those that fuel the initial growth of the pituitary.

Maturity, in some respects, brings diminished possibilities.

In spite of their importance, stem cells are hard to spot among the multitude of cells in com-

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plex tissue, according to the team of researchers led by scientists at Cold Spring Harbor Laboratory (CSHL).

Several years ago, neuroscientist Grigori Enikolopov, Ph.D., an associate professor at CSHL, and his colleagues developed a tool to look for stem cells that give rise to new adult brain cells.

Researchers knew that a gene called Nestin was active in these neural stem cells.

The CSHL team genetically engineered mice so that the same conditions that activate Nestin in a particular cell also make it glow green under ultraviolet light.

Using these mice gives researchers an important pointer to cells that may be adult stem cells.

Almost 100 research teams around the world have now used these special mice to help find adult stem cells in hair follicles, liver, muscle, and other tissues.

One place where stem cells had been suspected, but never found, is the pituitary gland.

This organ, which in people is about the size of a pea, sits at the base of the brain, where it secretes hormones that regulate various processes throughout the body.

In mice, the gland develops in the embryo, but then has a second growth spurt.

“A few weeks after they are born,” said Enikolopov, “the pituitary undergoes massive expansion” that suggests a role for adult stem cells.

Anatoli Gleiberman, Ph.D., a researcher in the lab of pituitary expert M. Geoff Rosenfeld at the University of California, San Diego, decided to work with the CSHL lab to look for pituitary stem cells.

The researchers used the Nestin-tracking mice to identify candidate cells in the anterior pituitary, the section of the organ that secretes hormones.

They then used other techniques to show that these are true stem cells.

“There are six main lineages in the adult pituitary,” Enikolopov said, “and we can demonstrate that one adult stem cell can generate all six lineages,” with each cell type secreting a different

hormone.

These cells differ from most adult stem cells, however.

“In most cases that we know,” Enikolopov said, “cells that become stem cells of the adult have been also contributing to embryonic development and continue to serve as stem cells in the adult.”

The research team demonstrated that adult stem cells in the pituitary did not help construct the embryonic organ.

Their research, the scientists said, indicates that the adult mouse pituitary includes two similar but not identical types of hormone-producing cells: some that grew in the developing embryo, and some that appeared later.

They speculate that having two sets of cells may let the organ respond differently to changing body conditions.

Therapeutic Potential?

Enikolopov said that hormones strongly influence human neuropsychiatric phenomena, including stress and depression, which are his main research focus.

“All are mediated through the pituitary,” he said, so changes that happen during the later growth of the gland could have lasting effects.

Does all of this have any potential use in psychiatry?

Is it possible that discovery of stem cells in the pituitary might someday lead to a way to alter human reactions to stress and stressful life events?

It’s way too early to tell.

Dr. Enikolopov said he and his colleagues are only beginning to delve into the consequences of what they’ve found.

“The pituitary is involved in response to stress and mood regulation,” he told us. “We believe that stem cells in the pituitary have a direct relevance to stress and depression. This is the [possible] connection of this work to psychiatry. We’re very much looking at the potential connection between stem cells in the pituitary and such

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things as stress, depression, and post-traumatic stress disorder.”

“At this point we wouldn’t say that we could treat the cells in the brain [that are involved in mood, stress, or depression],” he said.

His emphasis now is on better understanding of the interactions between the pituitary and other glands in the body, e.g., the adrenal, thyroid, gonads (sex glands), etc.

With better understanding of those processes, he said, “we will have a better handle on interfering with or correcting those physiological axes between the brain, pituitary, and the adrenal gland, let’s say, which produces corticosteroids, which then affect behavior and mediate stress.”

Somewhere in those processes stem cells may be playing a role, especially at times of profound physiological change, such as pregnancy or lactation

“Down the line we are testing whether stem cells contribute to the responses of the organism during profound physiological changes,” he said.

Dr. Enikolopov declined to speculate about potential stem cell-based therapies in this area.

“I think at this point it’s really too far away to talk about it,” he said. “We are looking at this from a new perspective. It could be that there is another layer of complexity: stem cells that are expanding in the tissue and sort of remodeling the tissue so that it responds to stress either more or less adequately. That’s the connection, but we are only starting here.”

Citation: “Genetic approaches identify adult pituitary stem cells;” Anatoli S. Gleiberman, Tatyana Michurina, Juan M. Encinas, Jose L. Roig, Peter Krasnov, Francesca Balordi, Gord Fishell, Michael G. Rosenfeld, and Grigori Enikolopov; *Proceedings of the National Academy of Sciences*; April 29, 2008.

The paper is available online at <http://www.pnas.org/cgi/doi/10.1073/pnas.0801644105>.

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Embryonic Stem Cells Used To Establish Tissue-Specific Blood Stem Cell Line

Swedish researchers have established and isolated the tissue-specific stem cells that produce blood cells (hematopoietic stem cells) by using genetically modified embryonic stem cells, it was announced on April 28.

Prof. Leif Carlsson led the research team at the Umeå Center for Molecular Medicine (UCMM) in Umeå, Sweden.

A deeper understanding of the regulation of blood stem cells is important if we are to be able to further develop treatments for diseases that require bone marrow transplants, such as leukemia, immune deficiencies, and anemia disorders.

Blood stem cells are unique in that they can both continually generate all types of blood cells and also produce new stem cells, so-called self-regeneration.

These two properties are the basic reason why we have a functioning blood system throughout our lives and why bone marrow transplants are a functional treatment method.

An understanding of how tissue-specific stem cells are produced and regulated is absolutely essential for us to be able to develop forms of treatment in so-called regenerative medicine, that is, where damaged tissue needs to be replaced by new tissue.

One source of transplantable cells for this purpose is embryonic stem cells, since they have a unique capacity to generate different types of tissues.

But one of the major problems with embryonic stem cells is to be able to establish and isolate tissue-specific stem cells, such as blood stem cells, from these cells in a reproducible manner.

Even though the process of self-regeneration is well known, the molecular mechanisms that underlie it are largely unknown.

The fact that it is now possible to establish and isolate blood stem cells from embryonic stem cells in a reproducible way will yield key insights into the molecular mechanisms that regulate the function of blood stem cells and will thereby lead to enhanced methods of treatment for patients who need bone mar-

(Continued on page 9)

row transplants, such as leukemia patients.

News released by Vetenskapsrådet (The Swedish Research Council).

Contact: The findings are published in *PLoS ONE* at <http://www.plosone.org/doi/pone.0002025>.

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Heart Progenitor Cells Developed From Embryonic Stem Cells

A team of international researchers has successfully grown human heart progenitor cells from embryonic stem cells, a significant step towards the creation of functioning heart tissue.

The advancement was announced by Canadian scientist Dr. Gordon Keller, director of Toronto's McEwen Centre for Regenerative Medicine at the University Health Network, and his team.

"This development means that we can efficiently and accurately make different types of human heart cells for use in both basic and clinical research," Keller said. "The immediate impact of this is significant as we now have an unlimited supply of these cells to study how they develop, how they function and how they respond to different drugs. In the future, these cells may also be very effective in developing new strategies for repairing damaged hearts, following a heart attack."

The study, a medical first, details supplying embryonic stem cell cultures with a series of factors that direct them to develop into immature heart cells, known as heart progenitor cells.

These progenitors are able to make three major cell types found in the human heart: cardiomyocytes, endothelial cells and vascular smooth muscle cells.

These three cell types are integral to the healthy function of the human heart.

The study created the cardiac cells by supplying embryonic stem cell cultures with a "cocktail" of growth factors involved in heart development, and then used surface markers to identify a unique precursor cell that is committed to heart development.

By isolating this novel cardiac stem cell and

supplying the right growth factors at the right time during development, they encouraged the cells to grow into cardiomyocytes, endothelial cells, and vascular smooth muscle cells, each an important constituent of the cardiovascular system.

The identification of this cardiac stem cell and the production of these three cell types will help researchers understand heart development in more detail, and provide an in vitro cardiac system for discovery and drug screening that is more natural and relevant to in vivo responses.

When the team transplanted this cardiac stem cell into mice with simulated heart disease, their heart function was significantly improved, offering hope to those aiming to develop this technique for treating human hearts.

"The achievement is another step toward generating and validating functional human heart cells at a scale and purity that is necessary for pharmaceutical discovery applications and for predictive toxicity screening of new drug candidates," said Dr. Ralph Snodgrass, CEO of South San Francisco, Calif.-based VistaGen, whose scientists participated in the study. "Furthermore this is a very good example of the use of key developmental switches and factors, combined with the identification and isolation of tissue committed precursors, to increase the efficiency and yield of mature cells critical to pharmaceutical applications."

VistaGen, a biotechnology company using ES cell technologies to discover and develop innovative drugs, expects to apply the results of this research to further develop its commercial applications of ES cell-derived cardiomyocytes in drug screening and predictive toxicology assays.

VistaGen has collaborated with Keller, one of the world's leading stem cell scientists, on research projects for more than 10 years.

In March, 2008, VistaGen announced an expansive new ES cell research alliance with UHN and the McEwen Centre.

Other collaborators in the landmark cardiac cell study included scientists from the Mount Sinai School of Medicine, Indiana University School of Medicine, the Weill Medical College of Cornell University, and London's Kings College Department of Infectious Diseases.

The full study can currently be found in the online version of *Nature*.

Entitled, "Human cardiovascular progenitor cells develop from a KDR1 embryonic-stem-cell-

(Continued on page 10)

derived population,” the study will also appear in the print edition in the coming weeks.

VistaGen uses of its proprietary embryonic stem cell technology platform to develop customizable, therapeutically focused drugs and drug development tools.

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Stem Cells From Human Hearts Develop Into Heart Muscle

Researchers in The Netherlands have succeeded for the first time in transforming large numbers of stem cells from adult human hearts into new heart muscle cells.

Until now, it was necessary to use embryonic stem cells to make this happen, the scientists said.

The findings by scientists at the University Medical Center Utrecht and the Hubrecht Institute were published in the latest issue of the journal *Stem Cell Research*.

The stem cells were derived from material left over from open-heart operations.

Researchers at UMC Utrecht used a simple method to isolate the stem cells from this material and reproduce them in the laboratory, which they then allowed to develop.

The cells grew into fully developed heart muscle cells that contract rhythmically, respond to electrical activity, and react to adrenaline.

“We’ve got complete control of this process, and that’s unique,” said principal investigator Prof. Pieter Doevendans, a professor of cardiology at UMC Utrecht. “We’re able to make heart muscle cells in unprecedented quantities, and on top of it they’re all the same. This is good news in terms of treatment, as well as for scientific research and testing of potentially new drugs.”

Doevendans will use the cultured heart muscle cells to study things like cardiac arrhythmia (abnormal heart rhythms).

Stem cells from the hearts of patients with

genetic heart defects can be grown into heart muscle cells in the lab.

Researchers can then study the cells responsible for the condition immediately.

Because they can also be used to test new medicines, research into genetic heart conditions can move forward at a much faster pace.

In the future, the researchers said, new heart muscle cells can likely be used to repair heart tissue damaged during a heart attack.

For some time now, it has been known that the heart is a source of stem cells.

Although in the past researchers from other countries have succeeded in using these cells to make heart muscle cells, this always required the presence of heart muscle cells from newborn mice or rats in the growth medium.

The stem cells discovered by the Dutch researchers were able to develop on their own.

Though heart muscle cells can be made from embryonic stem cells, the yield of cells is low because not all cells develop into muscle cells.

And ethical issues continue to make the isolation and harvesting of embryonic stem cells a controversial procedure.

Contact: University Medical Center Utrecht, <http://www.umcutrecht.nl/research>

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Scientists Around The Globe Confirm Value Of Menstrual Stem Cells

Scientists in the United States and Japan recently published studies independent of each other that confirmed the usefulness of stem cells derived from menstrual blood.

The Japanese study described a stem cell population that could not only become heart tissue in vitro, but could also repair injured hearts in animal models of heart attacks.

California company Medimmune Laboratories issued a statement saying that the Japanese study supported its own belief that menstrual stem cells have great potential.

The company has developed a version of those

(Continued on page 11)

cells, called "Endometrial Regenerative Cells (ERC), but they were not used in the Japanese study.

Meanwhile, a U.S. study examined to what degree Cryo-Cell International's menstrual cells could differentiate into a variety of cell lineages.

It described the multipotency of stromal stem cells present in connective tissues and in the endometrial tissues of the uterus.

"Stromal stem cells derived from menstrual blood exhibit stem cell properties, such as the capacity for self-renewal and multipotency," said Amit N. Patel, M.D., director of cardiac cell therapy at the University of Pittsburgh's McGowan Institute of Regenerative Medicine. "Uterine stromal cells have similar multipotent markers found in bone marrow stem cells and originate in part from bone marrow."

While collecting menstrual blood stromal cells directly from tissue would be invasive, according to Florida's Cryo-Cell, retrieving them during the menstrual cycle would not be.

"The ideal cell would also have the ability to be used in an allogenic manner from donors for optimal immunogenic compatibility," said Julie G. Allickson, Ph.D., Cryo-Cell's R&D chief. "Due to their ease of collection and isolation, MenSCs would be a great source of multipotent cells if they exhibit this property along with their ability to differentiate."

According to Thomas Ichim, CEO of San Diego, Calif.-based Medistem Laboratories, Inc. (MDSM), the Japanese study offers an unbiased confirmation of the presence of functional stem cells in the menstrual blood.

"Our previous publication and patent applications describe a cell population with phenotypic and functional similarities to the cells of [Japanese researcher] Hida," he said. "We are pleased to have aspects of our work successfully reproduced and advanced by scientists at the prestigious Keio University School of Medicine, Tokyo."

In November 2007, scientists led by Medistem announced the discovery of its version of the menstrual stem cell, the Endometrial Regenerative Cell.

The company said the menstrual blood-derived stem cell can differentiate into nine major tissues, produce high levels of therapeutic factors, and is capable of massive in vitro expansion.

Cryo-Cell also announced its discovery of MenSCs in November 2007.

According to Cryo-Cell, tests showed that MenSCs could differentiate into adipogenic, chondrogenic, osteogenic, ectodermal, mesodermal, cardiogenic, and neural cell lineages.

Patel said the sample MenSCs expanded rapidly and maintained greater than 50 percent of their telomerase activity when compared to human embryonic stem cells and better than bone marrow-derived stem cells.

"Studies have demonstrated that MenSCs are easily expandable to clinical relevance and express multipotent

markers at both the molecular and cellular level," Patel said.

Researchers emphasized the importance of the abundance and plasticity of MenSCs, Cryo-Cell said.

Based on the results of their studies, they noted the potential for MenSCs in regenerative transplantation therapies for many different organs and tissues.

"The need for regenerative therapies using cells with the ability to engraft and differentiate is vast," said Patel.

The Japanese study is "Novel Cardiac Precursor-Like Cells from Human Menstrual Blood-Derived Mesenchymal Cells;" Hida et al.; *Stem Cells*, 2008 Apr 17 [Epub ahead of print].

Patel's study was published in the most recent issue of *Cell Transplantation* (Volume 17, No. 3).

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Stem Cell Type Thought Crucial For Angiogenesis, Cancer Growth, Doesn't Exist - Study

Circulating endothelial precursor cells probably do not exist, researchers in the United States and Finland have found.

What's more, angiogenesis and cancer growth do not involve or depend on such hypothetical stem cells.

Angiogenesis, the growth of new blood vessels, is a central process in diverse physiological and pathological situations such as healing of wounds and traumas, cardiovascular disorders, inflammatory conditions such as rheumatoid arthritis, and in cancer growth.

The current belief about the source of blood vessel wall endothelial cells (ECs) responsible for vascular growth in adults is that a significant and crucial part of neovascular ECs originate from circulating stem and progenitor cells.

The cells are thought to be first mobilized from the bone marrow, and subsequently differentiate to mature bone fide ECs and incorporate in the vasculature.

This concept has become textbook material, and a common theme in modern vascular and cancer biology.

It is widely believed that tumor angiogenesis and cancer growth critically depend on bone marrow derived circulating endothelial precursor cells.

Endothelial precursors would thus provide a pow-

(Continued on page 12)

erful novel approach to block tumor angiogenesis and cure cancer.

Correspondingly, therapeutic transplantation of such stem cells would be a promising approach to restore tissue vascularization after ischemic events.

Clinical trials with human patients are currently ongoing based on the circulating endothelial precursor cell dogma.

Unfortunately, however, those precursor cells probably don't exist.

By using endothelial cell specific genomic mouse models and modern three dimensional cellular imaging technologies, researchers lead by Dr. Petri Salvén at the University of Helsinki, Finland, and Dr. Irving Weissman at Stanford University have shown that endothelial differentiation is not a typical function of bone marrow-derived stem cells, and it has to be an extremely rare event if it occurs at all.

However, angiogenic and tumor tissues contain large numbers of bone marrow-derived cells such as ordinary white blood cells that often are very close to blood vessel walls, and may therefore have been misinterpreted as blood vessel wall ECs in earlier studies utilizing less advanced technologies.

The results have great practical significance when researchers are trying to focus on novel approaches to cure cancer by targeting the normal cells of the body that supply

tumors with blood and nutrients.

"Our results will help the researchers to concentrate their efforts on molecular and cellular targets that actually exist" said Salvén, leader of the Helsinki team.

"It has been a learning experience to try to publish results that demonstrate that a number of fellow research have for years been studying nonexistent cells. Issues concerning publication bias and nonaccessibility of negative data are really becoming more and more relevant, just as recently seen also in other fields of biomedicine."

The research was published in the *Proceedings of the National Academy of Science* (PNAS, in press; online 21.-25.4)

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