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Volume 5, No. 16 | *News For Stem Cell Researchers & Laboratory Staff* | August 29, 2011

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The Latest News ...

Advanced Stem Cell Technology

Novel Antibody Combination Removes Tumor-Forming Cells From hESC-Derived Cells

Cells newly generated from human embryonic cells have an inherent problem: any remaining stem cells that haven't differentiated into the desired tissue can go on to become dangerous tumors called teratomas when transplanted into patients.

Now researchers have developed a way to remove these pluripotent human embryonic stem cells from their progeny before the differentiated cells are used in humans.

"The ability to do regenerative medicine requires the complete removal of tumor-forming cells from any culture that began with pluripotent cells," said Irving Weissman, M.D., director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine. "We've used a combination of antibodies to weed out the few undifferentiated cells that could be left in the 10 or 100 million differentiated cells that make up a therapeutic dose."

The scientists believe the technique could also be used to remove residual tumor-initiating cells from populations of cells derived from induced pluripotent stem, or iPS, cells. These cells may also be useful for therapy but, unlike embryonic stem cells, iPS cells are created in the laboratory from adult tissue.

"Commonly used differentiation protocols for embryonic

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stem and iPS cells often give rise to mixed cultures of cells," said research associate Micha Drukker, Ph.D., senior author of the study. "Because even a single undifferentiated cell harbors the ability to become a teratoma, we sought to develop a way to remove these cells before transplantation."

Teratomas are a jumble of tissues like teeth, hair and bone that owe their remarkable composition to the pluripotency of the cells from which they arise early in development.

In fact, the ability to form teratomas in animals is a defining feature of true pluripotent cells.

But the very feature that confirms a cell's pluripotency also makes it potentially dangerous to use therapeutically. That's why the researchers decided to try to develop an antibody that would recognize and bind to only pluripotent cells and enable their removal from a mixture of cells. Although a few such antibodies already existed, they were not specific enough on their own to completely weed out the tumor-causing cells.

The researchers studied two sets of antibodies – one commercially available and one they generated themselves – to identify which among them bound most strongly to pluripotent, but not differentiated, cells. They found one newly generated antibody that was highly specific for a previously unknown marker on undifferentiated cells that they termed stage-specific embryonic antigen-5, or SSEA-5.

The cells bound by this antibody, anti-SSEA-5, expressed high levels of pluripotent-specific genes and resembled embryonic stem cells in appearance. Anti-SSEA-5 also bound strongly to the inner cell mass of an early human embryo, the group of cells from which embryonic stem cell lines are derived.

When the researchers injected human embryonic stem cells recognized by anti-SSEA-5 into mice, they found that in seven out of seven times, the cells formed rapidly growing teratomas. However, cells that were not bound by anti-SSEA-5 formed smaller teratomas in only three of 11 experiments. Combining anti-SSEA-5 with two other antibodies known to bind to pluripotent cells completely separated the pluripotent from the differentiated cells, although the researchers did see some smaller, less-diverse growths in some cases.

Upon analysis, the researchers found that anti-SSEA-5 recognizes and binds to a cell-surface carbohydrate structure called a glycan. As the pluripotent cell differentiates, this glycan is modified to other glycan structures not recognized by the antibody.

"The study of glycans is becoming an active area of stem cell biology," said Tang. "Many glycans are highly expressed in embryonic stem cells, but not in differentiated cells. This warrants further study and may lead to new understandings about embryonic stem cell biology."

Stanford University has filed for patent protection for the use of monoclonal antibody-based protocols to remove teratogenic pluripotent stem cells from a cell mixture.

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Stem Cell *Lab World*

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http://dx.doi.org/10.1038/nbt.1947

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Laser Stimulation Of Stem Cells Reduces Heart Scarring After Heart Attack

A new treatment developed at Tel Aviv University uses laser-treated bone marrow stem cells to help restore heart function and health after a heart attack.

Heart attack or stroke causes heart scarring that can lead to dangerously paper-thin heart walls and a decreased ability to pump blood through the body.

Prof. Uri Oron of the Department of Zoology has developed and tested on animals an effective, non-invasive procedure that combines the therapeutic benefits of low-level lasers – a process called "shining" – and bone marrow stem cells that significantly reduces heart scarring after an ischemic event, in which the heart is injured by a lack of blood supply.

When the laser is applied to these cells a few hours after a heart attack, scarring can be reduced by up to 80 percent.

Oron's innovative method is ready for clinical trial.

Though the heart is known to contain some stem cells, they have a very limited ability to repair damage caused by a heart attack, Oron said, and researchers have had to look elsewhere.

One of the first efforts to use stem cells to reduce heart scarring involved harvesting them from the bone marrow and inserting them back into the heart muscle, close to the heart's blood supply, but this had limited success.

Oron, who has used low level lasers to stimulate stem cells to encourage cell survival and the formation of blood vessels after a heart attack, was inspired to test how laser treatments could also work to heal the heart.

He and his fellow researchers tried different methods, including treating the heart directly with low level lasers during surgery, and "shining" harvested stem cells before injecting them back into the body.

But he was determined to find a simpler method. After a low-level laser was "shined" into a person's bone marrow – an area rich in stem cells – the stem cells took to the blood stream, moving through the body and responding to the heart's signals of distress and harm. Once in the heart, the stem cells used their healing qualities to reduce scarring and stimulate the growth of new arteries, leading to a healthier blood flow.

To determine the success of this method, Oron performed the therapy on an animal model. Following the flow of bone marrow stem cells through the use of a fluorescent marker, the researchers saw an increase in stem cell population within the heart, specifically in the injured regions of the heart. The test group that received the shining treatment showed a vastly higher concentration of cells in the injured organ than those who had not been treated with the lasers.

In the longer run, Oron sees this as a way to make cell therapy simpler. Without the need to remove the stem cells from the body, this treatment stimulates a whole variety of stem cells to help heal the body: a "cocktail" ultimately more efficient than single-cell type treatments. This could prove to be beneficial to the repair of other human organs such as the kidney or the liver, he notes.

Although stem cells naturally heed the call to heal throughout the body, Oron said, their success tends to be limited without this laser treatment. But with treatment, the cells' effectiveness become much more highly enhanced.

"After we stimulate the cells with the laser

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Advertisement

and enhance their proliferation in the bone marrow, it's likely that more cells will migrate into the bloodstream. The cells that eventually reach the heart secrete growth factors to a higher extent, and new blood vessel formation is encouraged," Oron said.

Through these animal models, the non-invasive procedure has been proven safer and quicker than other options. He said that his team has also done a series of safety studies to rule out the possibility that the stimulation of the stem cells by laser could encourage the growth of abnormal tissues.

Under the specific and low doses of energy applied in this technique, no such dangers were found.

Citation: "Induction of autologous mesenchymal stem cells in the bone marrow by low-level laser therapy has profound beneficial effects on the infarcted rat heart;" Hana Tuby, Lidya Maltz, Uri Oron; *Lasers in Surgery and Medicine*, 2011; 43 (5): 401 DOI: 10.1002/lsm.21063.

Abstract:
http://dx.doi.org/10.1002/lsm.21063
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Stem Cells Cultured For A Week In Vitro May Improve Transplantation

New research finds that growing blood stem cells in the laboratory for about a week may help to overcome one of the most difficult roadblocks to successful transplantation, immune rejection. The study may lead to more promising therapeutic strategies for transplanting blood stem cells.

Hematopoietic stem cells (HSCs) are cells that can give rise to all of the different types of blood cells.

Transplantation of HSCs has been used to treat leukemia, lymphoma, and other types of cancer, as well as some autoimmune diseases. However, there is a significant risk that the transplanted cells will fail to be incorporated into the host, or that the new cells will be rejected by the immune system and the patient will develop life-threatening "graft-versus-host" disease.

Although scientists have identified some causes of transplant failure, many questions remain unanswered. "The resolution of these questions will promote the understanding of the immunology of blood-forming stem cells and other stem cells and greatly improve the practice of transplantation," said senior author Dr. Cheng Cheng Zhang from the University of Texas Southwestern Medical Center.

Zhang and colleagues had previously shown that they could successfully grow isolated mouse and human HSCs in the laboratory for transplantation and that there was a change in many of the proteins expressed on the surface of the cells. The researchers wondered whether this technique might change the functional properties of the cells as well and make them better suited for transplantation.

They were specifically interested in clinically relevant "allogeneic" transplants, transplants between individuals who are genetically different, including siblings and unrelated donor/recipient pairs.

Zhang's group transplanted freshly isolated HSCs or HSCs that were grown in the lab into mice and discovered that the HSCs that spent about a week growing in the lab were less likely to be rejected and more likely to be successfully incorporated into the recipient's blood.

The researchers went on to look at the mechanism that underlies this effect, and found that the lab-grown HSCs started to produce a specific immune system inhibitor on their surface that contributed to the improved transplantation efficiency.

"This work should shed new light on understanding the immunology of HSCs and other stem cells and may lead to development of novel strategies for successful allogeneic transplantation of human patients," Zhang said. "If donor human HSCs can be expanded in culture and engraft non-matched or low-matched patients without

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graft-versus-host disease, this strategy will possibly lead to an ultimate solution to problems in allogeneic transplantation."

The study was published in the August issue of *Cell Stem Cell*.

Citation: "Ex Vivo Expanded Hematopoietic Stem Cells Overcome the MHC Barrier in Allogeneic Transplantation;" Junke Zheng, et al.; *Cell Stem Cell,* August 2011, DOI: 10.1016/j.stem.2011.06.003

Article: Click here.
http://dx.doi.org/10.1016/j.stem.2011.06.003

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Scientists Create Neurons Directly From Human Skin Cells

Researchers have come up with a recipe for making functional neurons directly from human skin cells, including those taken from patients with Alzheimer's disease.

The new method may offer a critical short cut for generating neurons for replacement therapies of the future, according to new research.

Already, the converted neurons are beginning to yield insights into what goes wrong in the Alzheimer's brain and how diseased neurons might respond to treatment.

In earlier approaches to generate neurons from skin cells, those adult cells first had to be returned to an embryonic stem cell state. Those cells, called induced pluripotent stem (iPS) cells, are hard to come by – less than one percent of cells are typically reprogrammed successfully. In addition, the entire process is time-consuming, requiring months to coax cells into iPS cells and then stimulate them to become neurons.

"iPS cells are exciting given the limits on cloning and embryonic stem cells, but it is still a roundabout and lengthy process if the goal is to take patient cells or normal cells and use them as replacement cells," said Asa Abeliovich of Columbia University, senior author.

Not only are there efficiency issues, there is also an increasing concern about the stability of iPS cells, he said. Their ability to grow and produce any cell type makes them a cancer risk. Moreover, the cells may have limited use as models for understanding disease states because the processes used to derive them "may erase or overwhelm" the natural biology of the cells.

To get around these potential pitfalls, Abeliovich's team started with known transcriptional regulators and, through a process of trial and error, identified a cocktail of factors that could turn human skin cells into neurons. While the process was not initially very efficient, they refined the protocol, ultimately converting about 50 percent of the cells.

"It is a huge leap over the iPS-based process," he said. It is also more efficient than a similar method recently developed by another group.

When studied in a dish, the neurons derived from healthy skin cells could fire and receive signals, just like normal neurons. What's more, when placed into the brains of developing mice, the converted cells were able to connect up to the existing circuitry. "They really are neurons," Abeliovich said.

The method can also produce neurons from the skin cells of patients with a rare familial form of Alzheimer's disease (AD). The AD neurons superficially looked normal, but upon closer

(Continued on page 7)

inspection, Abeliovich's team saw abnormalities in the processing of amyloid precursor protein, the source for the amyloid plaques that riddle the brains of those with Alzheimer's disease. The neurons also showed more general differences in the way proteins inside the cell move around.

Abeliovich says that to really understand what goes wrong in Alzheimer's disease it will be important to look at what is happening in living human neurons. Earlier studies have been limited to exploring the consequences of the Alzheimer's mutations in tumor cells, skin cells or in mouse models of the disease.

Potentially the most exciting use of these Alzheimer's neurons will be for testing new drug candidates. Abeliovich notes that when the cells were treated with one existing candidate drug that reduces beta amyloid production, the protein 'trafficking' problem actually worsened, raising caution about that particular treatment. Going forward, his group plans to study neurons derived from skin cells from patients with the more common, sporadic forms of Alzheimer's disease.

"Sporadic disease accounts for 99 percent of cases and no one really knows if it is similar or different from the simpler genetic forms," Abeliovich said. "It's not a done deal that we'll be able to come up with answers, but at least we can now ask the question. In that sense, this is the tip of the iceberg."

The research was published in the August 5, 2011, issue of *Cell*.

Citation: "Directed Conversion of Alzheimer's Disease Patient Skin Fibroblasts into Functional Neurons;" Liang Qiang, et al.; *Cell*, 146, 359–371, 5 August 2011.

Article: http://dx.doi.org/10.1016/j.cell.2011.07.007

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Japanese Researchers Develop In Vitro Method Of Creating Sperm From Stem Cells

Researchers in Japan have developed a way to turn mouse embryonic stem cells into sperm.

The finding opens up new avenues for infertility research and treatment.

A Kyoto University team has coaxed mouse embryonic stem cells into sperm precursors, called primordial germ cells (PGCs), and shown that these cells can give rise to healthy sperm. The researchers say that such in vitro reconstitution of germ cell development represents one of the most fundamental challenges in biology.

When transplanted into mice that were unable to produce sperm normally, the stem cell derived PGCs produced normal-looking sperm, which were then used to successfully fertilize eggs.

These fertilized eggs, when transplanted into a recipient mother, produced healthy offspring that grew into fertile male and female adult mice. The same procedure could produce fertile offspring from induced pluripotent stem cells that are often derived from adult skin cells.

"Continued investigations aimed at in vitro reconstitution of germ cell development, including the induction of female PGCLCs and their descendants, will be crucial for a more comprehensive understanding of germ cell biology in general, as well as for the advancement of reproductive technology and medicine," the researchers wrote.

The article was published August 4, 2011, in *Cell* in a special online release.

Citation: "Reconstitution of the Mouse Germ Cell Specification Pathway in Culture by Pluripotent Stem Cells;" Katsuhiko Hayashi, et al.; *Cell*, 146, 1–14, 19 August 2011, DOI: 10.1016/j.cell.2011.06.052.

(Continued on page 8)

Article:
http://dx.doi.org/10.1016/j.cell.2011.06.052

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Scientist Converts Human Skin Cells Into Functional Brain Cells

A scientist has discovered a novel way to convert human skin cells into brain cells, an advancement that offers hope for regenerative medicine and personalized drug discovery and development.

Sheng Ding, Ph.D., of the Gladstone Institutes developed efficient and robust methods for transforming adult skin cells into neurons capable of transmitting brain signals, marking one of the first documented experiments for transforming an adult human's skin cells into functioning brain cells.

"This work could have important ramifications for patients and families who suffer at the hands of neurodegenerative diseases such Alzheimer's, Parkinson's and Huntington's disease," said Lennart Mucke, M.D., who directs neurological research at Gladstone. "Dr. Ding's latest research offers new hope for the process of developing medications for these diseases, as well as for the possibility of cell-replacement therapy to reduce the trauma of millions of people affected by these devastating and irreversible conditions."

The work was done in collaboration with Stuart Lipton, M.D., Ph.D., who directs the stem cell research Center at Sanford-Burnham Medical Research Institute.

Ding's work builds on the cell-reprogramming work of senior investigator Shinya Yamanaka, M.D., Ph.D. Yamanaka's 2006 discovery of a way to turn adult skin cells into cells that act like embryonic stem cells has radically advanced the fields of cell biology and stem cell research.

Ding's work extends Yamanaka's by offering still another method for avoiding the use of embryonic stem cells and creating an entirely new platform for fundamental studies of human disease. Rather than using models made in yeast, flies or mice for disease research, all cell-reprogramming technology allows human brain, heart and other cells to be created from the skin cells of patients with a specific disease.

The new cells created from the skin cells contain a complete set of the genes that resulted in that disease, representing the potential of a superior human model for studying illnesses, drugs and other treatments. In the future, such reprogrammed skin cells could be used to test both drug safety and efficacy for an individual patient with, for example, Alzheimer's disease.

"This technology should allow us to very rapidly model neurodegenerative diseases in a dish by making nerve cells from individual patients in just a matter of days, rather than the months required previously," Lipton said.

In the experiments, Ding used two genes and a microRNA to convert a skin sample from a 55-year-old woman directly into brain cells. (MicroRNAs are tiny strands of genetic material that regulate almost every process in every cell of the body.) The cells created by Ding's experiments exchanged the electrical impulses necessary for brain cells to communicate things such as thoughts and emotions. Using microRNA to reprogram cells is a safer and more efficient way than using the more common gene-modification approach.

In subsequent experiments, Ding hopes to rely only on microRNAs and pharmaceutical compounds to convert skin cells to brain cells, which should lead to more efficient generation of cells for testing and regenerative purposes.

The research was published online on July 28, 2011, in *Cell Stem Cell*.

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Reprogrammed Kidney Cells Could Someday Lessen Need For Transplants, Dialysis

Breakthrough research in two studies has found that patients' own kidney cells can be gathered and reprogrammed into progenitor cells that can form any cell type in the kidney.

Reprogramming patients' kidney cells could mean that in the future, fewer patients with kidney disease would require complicated, expensive procedures that affect their quality of life.

Approximately 60 million people around the world have chronic kidney disease, and many will need dialysis or a transplant.

In the first study, Sharon Ricardo, Ph.D. (Monash University, in Clayton, Australia) and her colleagues took cells from an individual's kidney and coaxed them to become progenitor cells, allowing the immature cells to form any type in the kidney.

Specifically, they inserted several key reprogramming genes into the renal cells that made them capable of forming other cells.

In a second study, Miguel Esteban, M.D., Ph.D. (Chinese Academy of Sciences, in Guangzhou, China) and his colleagues found that kidney cells collected from a patient's urine can also be reprogrammed in this way.

Using cells from urine allows a technology easy to implement in a clinic setting. Even better, the urine cells could be frozen and later thawed before they were manipulated.

If researchers can expand the reprogrammed cells – called induced pluripotent stem cells (iPSCs) – and return them to the patient, these iPSCs may restore the health and vitality of the kidneys. In addition to providing a potentially curative therapy for patients, the breakthroughs might also help investigators to study the causes of kidney disease and to screen new drugs that could be used to treat them.

In an accompanying editorial, Ian Rogers, Ph.D. (Mount Sinai Hospital, in Toronto, Ontario, Canada) noted that "together, these two articles demonstrate the feasibility of using kidney cells as a source of iPSCs, and efficient production of adult iPSCs from urine means that cells can be collected at any time."

The ease of collection and high frequency of reprogramming described in these articles may help improve future therapies in many other areas of medicine.

Citation: "Generation of Induced Pluripotent Stem Cells from Human Kidney Mesangial Cells;" Sharon Ricardo, et al.; *Journal of the American Society Nephrology*, 1 July 2011, 22: 1213-1220; published ahead of print May 12, 2011, DOI:10.1681/ASN.2010101022.

Abstract: http://doi.dx.org/10.1681/ASN.2010101022

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Citation: "Generation of Induced Pluripotent Stem Cells from Urine," Miguel Esteban, et al.; *Journal of the American Society Nephrology*, 1July 2011, 22: 1221-1228; published ahead of print June 2, 2011, DOI: 10.1681/ASN.2011010106

Abstract: http://doi.dx.org/10.1681/ASN.2011010106

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New Products

AMSBio Launches Chemically Defined SC Cryopreservation Solution

AMSBio is now offering Stem-CellBanker, a chemically defined freezing medium with optimized formulation for stem cells and iPS cells

(Continued on page 10)

storage as well as other valuable cells.

Supplied ready-to-use with a simple usage protocol, Stem-CellBanker is completely free of serum and animal derived components, and contains only European or U.S. Pharmacopoeia graded ingredients.

Part of the CellBanker series of cell freezing media, Stem-CellBanker significantly increases cell viability while maintaining cell pluripotency, normal karyotype and proliferation ability following resuscitation from cryopreservation, even after extended long-term storage. Independent research has demonstrated that hESC, MSCs and iPS cells cryopreserved with Stem-CellBanker produce significantly higher cell viability (> 90 percent) over conventional freezing medium, while retaining cell pluripotency, normal karyotype and proliferation ability.

Every batch of Stem-CellBanker cryopreservation medium is performance tested on Jurkat and SK-007 cells. Additional standard evaluations for endotoxins, pH, osmolarity and Mycoplasma contaminants are undertaken to ensure GMP equivalent quality.

The company also recently announced a new Web page that brings together technical articles written by the company and its customers.

Covering research areas including stem cell biology, apoptosis, cell invasion and migration, cell signaling, DNA damage, glycobiology, cell based assay technology and 3D cell culture techniques - the new resource has been set up to provide researchers with useful background reference information to assist them in their research.

Contact: http://www.amsbio.com/amsbio_whitepapers.aspx

Contact: http://www.amsbio.com/

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ProtoKinetix Launches AAGP As A Tool To Protect Cells In Research

Canada's ProtoKinetix (Vancouver, British Columbia) said it has completed the sale of AAGP (anti-aging glycopeptides) as a vital tool to protect delicate cells in the process of utilizing stem cells, to treat disease and injury.

This development will enable the company to ramp up sales of the unique AAGP family of molecules to the medical research community. This community includes major pharmaceutical corporations, universities, foundations, private laboratories, and government agencies.

Due to the extremely delicate nature and high cost of producing cells typically used in medical research, the protection and defense of these cells is a critical priority in any successful research program.

AAGP has demonstrated superior properties of protection in the face of a wide range of hostilities. Data shows that the addition of this family of molecules will substantially increase the viability and longevity of these critical cells, resulting in a cost reducing, shorter research cycle.

While the primary focus of ProtoKinetix internally is the development of disease specific therapeutic agents, this opportunity to commence cash flow will enhance the company's ability to expand its therapeutic targets.

Last month. The company selected the University of British Columbia to study the ability of AAGP to suppress eye inflammation.

ProtoKinetix' management believes that these studies will lead to the development of an effective non-steroidal anti-inflammation treatment. This multi-billion dollar market is just the first of the many applications that ProtoKinetix intends to exploit as a platform for therapeutics targeting specific diseases. Inflammation is the cause of destruction of otherwise healthy tissues and organs.

Inflammation of the eye has many causes

(Continued on page 11)

including viruses, bacteria and auto-immune diseases such as rheumatoid arthritis. If left untreated, the inflammation can lead to glaucoma, cataracts and total loss of vision. Current treatments include the frequent and constant use of topical corticosteroids that have potentially serious health issues.

Upon proving up this low risk and powerful anti-inflammation agent, ProtoKinetix believes that AAGP will become the therapy of choice for inflammatory eye disease.

Contact: http://www.protokinetix.com

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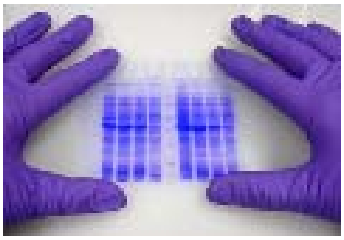

Stem Cell Lines

NIH Okays Four BioTime GMP Human Embryonic Stem Cell Lines

BioTime, Inc., of Alameda, Calif., announced that four human embryonic stem (hES) cell lines: ESI-035, ESI-049, ESI-051 and ESI-053, developed by a BioTime subsidiary have been approved by the National Institutes of Health (NIH) for inclusion in the NIH Human Embryonic Stem Cell Registry.

This approval opens the door to the use of these cell lines in federally funded research. BioTime previously announced the inclusion of ESI-014 and ESI-017 to the NIH Human Embryonic Stem Cell Registry.

"We believe these six human embryonic stem cell lines now approved for federal funding are the largest set of GMP-compliant lines available to U.S. researchers," said CEO Michael West. "As researchers work towards developing therapeutics for use in hard-to-treat diseases, we believe that our clinical grade hES cell lines will enable them to easily translate scientific progress into commercially successful therapeutic products."

ESI-035, ESI-049, ESI-051 and ESI-053 were developed by ES Cell International Pte. Ltd. (ESI), a wholly owned subsidiary of BioTime. ESI is one of the earliest pioneers of human embryonic stem cell technology.

The ESI hES cell lines were derived using procedures and documentation that are in compliance with current Good Tissue Practices (cGTP) and current Good Manufacturing Practices (cGMP), are free of animal feeder cells and have been assessed for pluripotency and karyotypic stability.

In collaboration with the California Institute of Regenerative Medicine, BioTime has supplied research grade versions of these lines to dozens of researchers throughout California, including those in the University of California system. BioTime has agreed to provide the complete genome sequence to the public by the fall of 2011 to facilitate the development of products derived from these cell lines. One of the ESI cell lines is being evaluated by a large pharmaceutical company for potential use in its product development program.

The NIH created the Human Embryonic Stem Cell Registry in 2001 to facilitate research using human embryonic stem cells. The registry includes hES cell lines that meet certain eligibility criteria including ethical derivation and informed consent. Only research projects using hES cell lines listed in the Registry are eligible for federal funding.

Contact: Researchers interested in obtaining the hES cell lines ESI-035, ESI-049, ESI-051 and ESI-053 should visit

http://www.biotimeinc.com

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Finance & Funding

Hamilton Thorne: Proposed Private Placement Of $3 Million Of Common Shares

Beverly, Mass.-based Hamilton Thorne Ltd., a provider of advanced laser systems for the regenerative medicine, fertility and stem cell research markets, on August 8 announced that it is proposing to issue, on a private placement basis, an aggregate of up to approximately 12,000,000 common shares of the company at CDN$0.25 per common share, for gross proceeds of up to approximately US$3 million (subject to increase at the discretion of the board of directors).

The company anticipates that up to approximately 9,600,000 Common Shares representing gross proceeds of up to approximately US$2.4 million will be issued to insiders of the company.

The private placement is subject to the approval of the TSX Venture Exchange and was expected to close in mid-August 2011.

The company also announced that it will be offering the holders of its convertible subordinated debentures issued in August 2010 and March 2011, the right to convert, subject to receipt of all applicable TSX-V approvals, the principal amount of such debentures, including all accrued interest, into common shares, at the conversion price specified in such debentures, in advance of the maturity date of such debentures. At this date, the holders of approximately CDN$1.3 million of outstanding debentures have indicated their intention to convert such debentures and accrued interest into approximately 7,100,000 common shares.

Each such holder is also an insider of the company. If all remaining debenture holders convert their debentures and accrued interest, the company expects to issue up to approximately 2,800,000 additional common shares. The conversion of all accrued interest into common shares is also subject to TSX-V approval.

The company intends to use US$1.5 million of the net proceeds of these transactions to reduce the amount outstanding on the company's bank line of credit from US$5 million to US$3.5 million. The balance will be used to fund the company's research and development, and to provide working capital.

"This transaction will strengthen our balance sheet by reducing our debt position by a minimum of US$2.8 million, reduce interest expense by nearly US$200,000 per year and provide us with the capital to accelerate our investments in research and development," said CEO Meg Spencer. "Hamilton Thorne's newly launched laser and fertility products have already generated strong interest from our customer base in the first half of 2011, and this infusion of capital will enable us to focus on key growth markets such as advanced cell biology, gene expression and cancer research markets."

Contact: http://www.hamiltonthorne.com

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Strategic Alliances

Organizations Collaborate To Improve Umbilical Cord Blood Stem Cell Characterization

ImageIQ, Inc., (Cleveland, Ohio) announced that it will partner with three Ohio research organizations to develop customized image acquisition and analysis software as part of the three-year biomedical technology and innovation project through an Ohio Third Frontier Program

(Continued on page 13)

grant.

The software, initially developed in conjunction with researchers at Cleveland Clinic, will be custom-tailored by ImageIQ to extract specific stem cell performance measurements that are important for assessing whether or not a cord blood unit should be banked and cryopreserved for future clinical use. ImageIQ provides custom-tailored preclinical and clinical imaging analytics, software engineering and visualization services for research, medical device and pharmaceutical organizations.

Organizations participating in the collaboration include the National Center for Regenerative Medicine (NCRM) at Case Western Reserve University (CWRU), Cleveland Clinic and the Cleveland Cord Blood Center (CCBC)

ImageIQ will use its extensive cell biology, image analysis and software engineering expertise to develop automated quantitative image analysis software, which will be coupled with a cell culture imaging technology and initially deployed at the Cleveland Cord Blood Center. The project includes ImageIQ developing an innovative imaging and image analysis technology for assaying the quality of umbilical cord blood units prior to cryopreservation and subsequent therapeutic application. The project is a collaborative effort among the NCRM, the Clinical Tissue Engineering Center (CTEC), CCBC and ImageIQ.

In addition to oversight, the Ohio Third Frontier Program will provide the necessary funding to execute the project over the course of three years. The Ohio Third Frontier is also a direct source of funding for both CTEC and NCRM. NCRM will provide administrative support for all of the program collaborators.

"This project highlights the depth and diversity of expertise in stem cell biology and cell therapy that is available in Cleveland, and the rich collaborative environment that we have established in Northeast Ohio," said George Muschler, M.D., Orthopedic Surgeon, Director of CTEC and the Principal Investigator for Cleveland Clinic. "The complex nature of our stem cell research and technology development programs necessitates a custom, application-specific approach to characterizing stem cells using image analysis and visualization. Pairing our stem cell biology expertise with ImageIQ's experience in utilizing custom imaging and image analysis to improve stem cell research will enable our team to develop a truly valuable technology."

CTEC, NCRM and CCBC will leverage more than a decade of cell-based life science research experience that the ImageIQ team garnered during its tenure within Cleveland Clinic, where it functioned as the Biomedical Imaging and Analysis Core.

"We are enthused to have been chosen by the CTEC and CCBC to support such a unique technology development program," said Dr. Amit Vasanji, chief technology officer at ImageIQ. "Our unique combination of stem cell imaging, image analysis, and software engineering expertise, and our ability to accelerate R&D and product development timelines will significantly enhance the work associated with this important collaboration."

The use of umbilical cord blood stem cells as a starting material for stem cell research and therapies has steadily increased over the past decade.

Contact: http://www.Image-IQ.com
Contact: http://www.ncrm.us
Contact: http://www.ctecohio.org
Contact:
http://www.clevelandcordblood.org

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Events

Seminar Series On Combining Cell Biology And Molecular Genetics

Fluidigm Corporation of South San Francisco, Calif., (FLDM) said earlier this month that it would collaborate with BD Biosciences, a segment of BD (Becton, Dickinson and Company), to co-host a public seminar series on the isolation and analysis of single cells.

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Entitled "A Powerful Technique for Single-Cell Analysis," the seminars will showcase cell isolation using the BD FACSAria III Cell Sorter and analysis using the Fluidigm BioMark HD System.

The combination of both the cell surface phenotype obtained from cell sorting and the gene expression profiles of individual cells isolated from a heterogeneous population of cells provides a deeper view into cellular systems.

Utilizing cellular and molecular biology to profile single-cell populations alleviates the complexity caused by cell heterogeneity.

BD cell sorting systems (such as the BD FACSAria III Cell Sorter) provide scientists the flexibility to isolate single cells of interest from thousands of cells in a population using up to 18 surface markers.

Assessment of cellular heterogeneity and the cellular bimolecular processes is obtained by assaying for differential expression levels using the Fluidigm BioMark HD System.

The seminar series will discuss the experimental workflows of both companies' technologies – BD FACSAria III Cell Sorter and the Fluidigm BioMark HD System – that reveal cell population heterogeneity. These public seminars are being held in the San Francisco Bay Area, Boston, New York City, Houston and Montreal, in addition to a number of private institutions throughout North America.

Contact: http://www.fluidigm.com

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