STEM CELL lab world

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- Preclinical research
- Cells (human, animal)
- Culture media, reagents, etc.
- Research equipment
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Top of the News...

British Scientists Develop Stem Cell Tools That Could Aid Drug Development

Scientists in the UK have designed, developed and tested new molecular tools for stem cell research to direct the formation of certain tissue types for use in drug development programs.

A collaborative team of scientists from Durham University and the North East England Stem Cell Institute (NESCI) have developed two synthetic molecules which can be used to coax stem cells to "differentiate" (transform into other forms of tissue).

Stefan Przyborski

Their use could also help reduce the number of animals used in laboratory research, they said.

The team's results are published in the current issue of the scientific journal, *Organic and Biomolecular Chemistry*.

The new molecules, called EC23 and EC19, have been found in robust scientific tests to be far more stable than the naturally-occurring molecule currently used to induce stem cells to differentiate in the laboratory, known as All-trans-retinoic Acid (ATRA).

Their use will thus improve the reliability of experiments.

The scientists, who tested the effectiveness of EC23 and EC19 on four types of stem cells, say it is also significant that each individual synthetic molecule has been found to be more effective at causing the cells to transform into specific types of tissue.

For example, EC23 was found to be particularly effective at producing neurons (nerve cells) which can be used in laboratory testing for drugs for brain disorders such as Alzheimer's disease and Parkinson's disease.

In contrast, EC19 was found to be particularly effective at producing epithelial cells – the cells that line the inner and outer surfaces of the body.

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Stem cells are a special type of cell that has the ability to renew other cells in the body.

One of the challenges facing stem cell scientists is to find out how these may be reprogrammed to become different tissue types.

The team consisted of synthetic chemists, Dr. Andrew Whiting and Prof. Todd Marder and stem cell biologist, Dr. Stefan Przyborski and their research groups at Durham University, who are all members of the North East England Stem Cell Institute (NESCI).

They also worked with spin-out company Reinnervate; local SME, High Force Research Ltd and Newcastle University.

"The key thing about these synthetic molecules is that they remain stable and are exactly the same every time you use them, ensuring more reliable scientific experiments compared to those which use ATRA," Przyborski said.

Stem Cell *Lab World*

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"Because the results will be more scientifically robust, this will accelerate drug development using human stem cell-derived tissues and potentially reduce the numbers of animals used in such research.

"Another significant characteristic of these synthetic molecules is that they direct stem cells down specific pathways, meaning that they, individually, will be useful for very specific types of drug development work. EC23, for example, produces almost 40 per cent more neurons than ATRA."

"We've set out to make stable mimics of natural compounds which control cell development," Whiting said, "but in this case, not only have we uncovered a compound which is not only stable and does what the natural system does, but it actually seems to be better as well. It's a real bonus and shows the validity of the approach."

Przyborski, who is also director and chief scientific officer of spin-out company Reinnervate Limited, is marketing EC23 through Reinnervate.

He said the results showed that synthetic retinoids EC23 and EC19 could be used to replace All-trans-retinoic acid (ATRA).

ATRA is sensitive to light, heat and air, and exposure to light especially causes it to degrade rapidly, meaning scientists are never sure exactly what concentration or what mixture of isomers they are working with.

The experiments on EC23 and EC19, which included highly detailed analysis by nuclear magnetic resonance (NMR) showed that these synthetic molecules were not sensitive to light and therefore did not degrade.

The scientists are now developing a "molecular toolkit" of synthetic compounds which are tailor made for specific stem cell and drug development work.

The project was funded in part by Reinnervate, the regional development agency, One NorthEast, Durham University, High Force Research Ltd., NESCI, and by research councils the MRC, EPSRC, BBSRC.

Through a related collaboration with Durham University polymer chemist, Prof. Neil Cam-

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Advertisement

eron, Reinnervate is also marketing a unique plastic scaffold to drug developers that allows stem cells and other tissue to be grown in the laboratory in conditions similar to the way they grow in the human body.

Extensive tests have shown the technology is a cheap and straightforward way of cultivating cells in three-dimensional forms.

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Researchers Create New Stem Cell Screening Tool

Scientists in Israel have reported a breakthrough on a new classification system for identifying human pluripotent stem cells that have the potential to differentiate into every cell type in the human body.

Igor Ulitsky

"There is a huge interest in scientists taking skin cells or other body cells of a person, and then turning them into stem cells for creating new neurons in the brain," said Igor Ulitsky, a Ph.D. student in the Blavatnik School for Computer Science, Tel Aviv University. "Using a person's own stem cells is both ethically acceptable, and in some cases even better for regenerating tissue than embryonic stem cells."

Tel Aviv University research played a central role, creating new bioinformatics algorithms to analyze the data and put together the pieces of the puzzle.

The result is, in effect, an encyclopedia describing different stem cell types and their characteristics.

Using a collection of about 150 human stem cell samples, the researchers created a database of global gene expression profiles and discovered that all of the pluripotent stem cell lines showed a remarkable similarity in the analysis, while other cell types were more diverse.

The analysis by Shamir's lab revealed a protein-protein network common to pluripotent cells, pointing to what may be one of the key building blocks of the machinery that enables these transformative cells to differentiate into multiple cell types.

Before this breakthrough, made possible by international collaboration, scientists were baffled by how to distinguish different stem cell types.

"Our lab helped devise a method to classify stem cells according to their machinery," Ulitzky said. "Stem cells have small but significant differences between them, and knowing the potential properties of each kind is valuable for advancing this promising field of research."

With rapid advances in the field of stem cells – including methods to induce pluripotence in various cells, such as those that comprise human skin – the question of how to define pluripotence has become increasingly critical.

This is especially the case for human cell lines, which for both ethical and scientific reasons cannot be treated as those from other species.

"There has been no ethically acceptable equivalent test that could prove pluripotency in human cell preparations," said Franz-Josef Mueller, M.D., an investigator at Scripps. "Many have been purported to be multi- or pluripotent, but there has been no practical way to define pluripotency in human cells."

Next, the researchers plan to investigate the regulation of this protein network and how it might be used to advance the development of human gene therapies.

The study, published in the journal *Nature*, was supported by several grants including the Edmond J. Safra Bioinformatics Program and the Raymond and Beverly Sackler Chair in Bioinformatics at Tel Aviv University.

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UK Firm Creates First Authentic Rat Embryonic Stem Cells

Stem Cell Sciences plc (AIM:STEM, ASX:STC) of Cambridge, England, said on September 2 that two independent laboratories in the UK and the United States have achieved germ-line transmission from embryonic stem (ES) cells in rats using technologies exclusively licensed to the company by Edinburgh University.

"This is believed to be the first time that germ-line transmission from rat ES cells has been demonstrated, and full scientific reports on this breakthrough, which has been independently verified, have been submitted to a major scientific journal for publication," the company said in a statement.

Under the terms of its agreement with Edinburgh University, SCS has global exclusive rights to commercialize the rat ES cells, the specific culture medium used to generate and grow the cells, and rats derived from them.

The company has exclusively licensed two important patents covering this new technology from the University and now plans to engage in confidential discussions with interested parties seeking a sublicense to use rat ES cells in their commercial drug discovery programs.

The main advantage of this important new technology is that it allows the generation of both knock-out rat models, in which the effect of gene deletion is studied, as well as the generation of knock-in models, which involves the insertion of genes.

For example, in the case of knock-out models, their response to drugs can provide information on safety and efficacy.

Alternatively, the insertion of genes such as those involved in drug metabolism in the human liver means that knock-in models can provide information on human safety and pharmacokinetics.

"This remarkable breakthrough will enable the generation of transgenic rat models for drug discovery in a very similar manner to the already widely used transgenic mice models," said CEO Alastair Riddell. "The advantage here is that rats are viewed as more predictable human models than mice for several psychiatric, neurological and cardiovascular drug targets. The ability to knock-in human genes should also enable drug metabolism studies to be undertaken with higher predictability in rats than previously available. We believe this opens the way to new and more effective drug discovery, and expect there to be considerable commercial interest in access to this exciting technology."

The culture medium patent family (PCT/GB2007/001163), which is filed in multiple territories including the United States, contains several specific enzyme inhibitors, which, when used in certain combinations, can be used to grow embryonic (or pluripotent) rat stem cells reliably in a serum-free environment.

The rat ES cell patent family (PCT/GB2007/002913), which is also filed in multiple territories including the United States, gives SCS the exclusive right to make and commercialize unique rat models for biopharmaceutical research and development, a global market with an estimated size in excess of $80 million.

Stem Cell Sciences (SCS) is focusing on the commercial application of stem cell biology technologies for drug discovery and regenerative medicine research.

Contact: http://www.stemcellsciences.com

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Embryome Licenses Virus-Free iPS, ESC Differentiation Technology

Alameda, Calif.-based Embryome Sciences, Inc., a subsidiary of BioTime, Inc. (BTIM) , said on August 21 that it has licensed a portfolio of patents and patent applications from Advanced Cell Technology, Inc. relating to induced pluripotent stem cells (iPS cells) and embryonic stem

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cell differentiation technology.

The license is for the commercialization of products in human therapeutic and diagnostic product markets.

The technology licensed by Embryome Sciences covers methods for the transformation of cells of the human body, such as skin cells, into an embryonic and pluripotent state.

Pluripotent means that the cells have the potential to become any kind of cell found in the human body.

Because this iPS technology does not involve human embryos or egg cells, and classical cloning techniques are not employed, the use of iPS technology may eliminate ethical concerns that have been raised in connection with the procurement and use of human embryonic stem cells in scientific research and product development.

This type of cell derivation may also prove to be more practical for the commercial production of stem cell products than previous methods.

The portfolio of patents and patent applications licensed by Embryome Sciences covers methods to produce iPS cells that do not carry the viral vectors or added genes.

Other iPS technology, currently being practiced by other researchers, utilizes viruses and genes that are likely incompatible with human therapeutic uses.

Embryome Sciences believes that technologies that facilitate the reprogramming of human cells to iPS cells without using these viruses could be advantageous in the development of human stem cell products for use in medicine and are, therefore, important advancements in the field.

Sublicensed from ACT for all human therapeutic and diagnostic applications are US patent application numbers 10/032,191, titled "Methods for cloning mammals using reprogrammed donor chromatin or donor cells," and 10/910,156, "Methods for altering cell fate." These patent applications relate to technology to alter the state of a cell, such as a human skin cell, by exposing the cell's DNA to the cytoplasm of another reprogramming cell with differing properties.

In a second series of patent applications licensed nonexclusively from ACT for use in commercializing the previously-mentioned patents are technologies for the use of reprogramming cells that overexpress RNAs for the genes OCT4, SOX2, NANOG, cMYC, LIN28, and other factors known to be useful in iPS technology (PCT/US2006/030632), methods of resetting cell lifespan by extending the length of telomeres (10/790,640 and 11/079,930), the use of the cytoplasm of undifferentiated cells to reprogram human cells (PCT/US2000/018063), the use of hemizygous HLA O- stem cells for blood and other cell banking (PCT/US2006/040985), methods of screening for differentiation agents (PCT/US02/26945), and stem cell-derived endothelial cells modified to disrupt tumor angiogenesis (11/228,549).

"These technologies, when combined with our existing intellectual property, give us a path to create patient-specific stem cells of any kind without the difficulties of current iPS approaches," said Embryome CEO Michael West. "Our license of the iPS technology adds to our portfolio of in-licensed embryonic stem cell patent licenses that includes the core technology from the Wisconsin Alumni Research Foundation (WARF), and other technology sublicensed from Lifeline Cell Technology, LLC and Advanced Cell Technology, Inc. We plan to use the newly-acquired technologies in developing and marketing additional near-term stem cell products."

The license package also includes US application #11/025,893, titled "Method of differentiation of morula or inner cell mass cells and method of making lineage-defective embryonic stem cells" that contains technology useful in producing embryonic progenitor cells without the utilization of embryonic stem cell lines.

In addition, US application #s 11/028,345, 11/211,174 and 11/478,780, called "Novel culture systems for ex vivo development," contains technology for utilizing avian cells in the production

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of stem cell products free of viruses and bacteria.

These patent applications were licensed to Embryome Sciences exclusively for all applications other than drug testing, commercial research use, and use in the diagnosis or treatment of human diabetes, liver diseases, retinal diseases and retinal degenerative diseases, which are covered by a license from ACT to Lifeline Cell Technology, LLC.

Embryome Sciences and Lifeline are already parties to an agreement for the production of commercial research products, which may include products using this technology.

Embryome Sciences is presently marketing cell growth media called ESpan in collaboration with Lifeline.

These growth media are designed for the culturing of human embryonic progenitor cells.

Additional new products that Embryome Sciences has targeted for development are ESpy cell lines, which will be derivatives of human embryonic stem cells that send beacons of light in response to the activation of particular genes.

The ESpy cell lines will be developed in conjunction with Lifeline using ACTCellerate technology licensed from ACT and other technology sublicensed from Lifeline.

Embryome Sciences also plans to bring to market new growth and differentiation factors that will permit researchers to manufacture specific cell types from embryonic stem cells, and purification tools useful to researchers in quality control of products for regenerative medicine.

BioTime is developing blood plasma volume expanders, blood replacement solutions for hypothermic (low temperature) surgery, organ preservation solutions, and technology for use in surgery, emergency trauma treatment and other applications.

BioTime's lead product Hextend is manufactured and distributed in the United States by Hospira, Inc. and in South Korea by CJ Cheil-Jedang Corp. under exclusive licensing agreements.

Contact: http://www.biotimeinc.com

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Scientists Generate "Clinical-Scale" Red Blood Cells From hESCs

"Inexhaustible" Supply Of Transfusion Cells?

Advanced Cell Technology, Inc., (OTC: ACTC.PK) of Worcester, Mass., said on August 19 that mature human embryonic stem cells (hESCs) can be differentiated into functional oxygen-carrying red blood cells (RBCs) under conditions suitable for scale-up.

The research by ACTC and its collaborators at the Mayo Clinic and the University of Illinois appears online in the journal *Blood.*

For the first time, the scientists reported, the oxygen-carrying capacity of hESC-derived blood cells is comparable to normal transfusable RBCs, and the cells respond to biochemical changes in a physiologically effective manner.

"Limitations in the supply of blood can have potentially life-threatening consequences for patients with massive blood loss," said Robert Lanza, M.D., the top scientist at the company and senior author of the study. "Embryonic stem cells represent a new source of cells that can be propagated and expanded indefinitely, providing a potentially inexhaustible source of red blood cells for human therapy. We can currently generate 10 to 100 billion red blood cells from a single six-well plate of stem cells. The identification of a stem cell line with blood-type O would permit the production of compatible 'universal donor' blood. We also have work underway to generate reprogrammed (iPS) stem cells from individuals with universal-donor blood."

Efficient, controlled differentiation of hESCs into homogeneous RBC populations has not been previously achieved, the company said.

The research paper describes for the first time the generation of RBCs from hESCs with oxygen-transporting capacity, and that the functional properties of these cells are similar to those

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of normal erythrocytes.

Multiple stem cell lines were stimulated to undergo differentiation in vitro to form functional RBCs (blood types A, B, O, and both RhD+ and RhD-) on a large scale under conditions suitable for scale-up and clinical translation.

Although alternative sources of progenitors for the generation of large-scale transfusable RBCs have been investigated, including cord blood, bone marrow and peripheral blood, it is clear that even after expansion and differentiation, these sources represent donor-limited sources of RBCs.

Moreover, the low prevalence of O(-) type blood in the general population further intensifies the consequences of blood shortages for emergency situations and battlefield trauma care, where the need for blood typing can imposes serious delays in initiating transfusions

Another critical issue for clinical utilization of hESC-derived RBCs is whether they can be enucleated in vitro.

"We show that up to 65 percent of the blood cells underwent multiple maturation events that resulted in the extrusion of the nucleus," said Shi-Jiang Lu, Ph.D., of ACT and first author of the paper. "They formed enucleated erythrocytes with a diameter of 6-8 (mu)m, which is similar to normal red blood cells. We also showed that the cells could express adult (beta)-globin and respond normally to biochemical changes."

Contact: http://bloodjournal.hematologylibrary.org/papbyrecent.dtl

Contact: http://www.advancedcell.com

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ISC Corp. Inks Manufacturing Agreement With Millipore

Oceanside, Calif.-based International Stem Cell (ISCO) said on September 9 it has entered into a worldwide distribution agreement with Millipore Corporation (MIL) to manufacture living cells and cell culture products to be sold through Millipore's distribution network.

International Stem Cell has perfected a method of creating human stem cells from unfertilized eggs.

These cells, called "parthenogenetic" stem cells promise to alleviate two critical problems inherent in cell transplantation today, immune rejection and the ethical issues associated with the use of fertilized human embryos.

ISCO, through its wholly-owned subsidiary, Lifeline Cell Technology (Walkersville, Md.) develops and manufactures cell culture products for research use. Such manufacturing generates revenue and therapeutic production capacity for ISCO.

Millipore provides technologies, tools, and services for bioscience research and biopharmaceutical manufacturing.

International Stem Cell has developed pluripotent human stem cells from unfertilized human eggs, as well as techniques to cause those stem cells to be "differentiated" into the specific cell types required for transplant.

Contact: http://www.internationalstemcell.com

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Georgia Firm Licenses Technology For hESC-Derived Mesenchymal Cells

ArunA Biomedical, Inc., of Athens, Georgia said on August 19 it has received an exclusive license from the University of Georgia Research Foundation that will enable the company to commercialize human mesenchymal cells developed at the school.

The cells (hMSC), derived from human embryonic stem cells, have never been available, the company said.

ArunA will offer the academic and industrial research communities access to a highly uni-

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form population of human mesenchymal cells grown as adherent monolayer cultures in multiple turn-key kit formats.

The hMSC kits will provide a physiologically relevant and genetically stable source of research material for use in a broad range of life science research applications such as: developmental pathway studies, disease modeling, in vitro toxicology, compound screening and humanized animal models.

"ArunA's proprietary adherent monolayer culture technology creates millions of highly uniform cells. These unique cells provide researchers with new enabling tools that can have a measurable impact on the advancement of drug discovery," said CEO William Sharp. "We are targeting an early first quarter 2009 launch of ArunA's first hMSC kit."

"One of the most important uses of human embryonic stem cells will be in the generation of uniform populations of adult stem cells and progenitor cells," said Robert Nerem of the Georgia Institute of Technology. "It is thus exciting that ArunA Biomedical will be able to provide uniform cell populations of human mesenchymal cells in kit form. This not only will be of value to bench scientists, but also in advancement toward clinical therapies."

Privately held ArunA is focused on commercializing new technologies in human stem cell research for use in drug discovery and basic research.

Contact: http://www.arunabiomedical.com/

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Publications

New Guidelines: Immunoassays; Flow Cytometry, Solid Phase Assays

Wayne, Pa.-based Clinical and Laboratory Standards Institute (CLSI) recently published guidelines in the area of immunology and ligand assay .

The document provides guidance for assessing analytical performance, methods comparison, and clinical accuracy of laboratory tests.

It focuses on unique characteristics of immunoassays, and provides a guide to designing, executing, and analyzing a clinical evaluation.

"The updated information provides a must-have resource for specialty laboratories, industry, and developers of assays. It is a terrific reference document," said Marilyn M. Lightfoote, M.D., Ph.D., Food and Drug Administration (FDA) Center for Devices and Radiological Health, and chairholder of the working group that developed the guideline.

The elements of this guideline include:

– a development plan for an effective analysis and evaluation;
– a discussion of the planning and design considerations that are necessary for a successful evaluation;
– a description of requirements for conducting the evaluation through monitoring and database management; and
– a brief review of the analytical performance measures that must be in place before testing clinical specimens.

This document replaces the first edition of the approved guideline, I/LA21-A, which was published in 2002.

It includes the following updates:

– specific details on selection and use of test specimen panels;
– specimen library collections;
– reference panels including specimen commutability issues;
– sample size considerations for evaluation studies; and
– an appendix to guide the user in sample size selections.

Clinical Evaluation of Immunoassays; Approved Guideline–Second Edition (I/LA21-A2)

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will aid developers of "in-house" assays for institutional use, developers of assays used for monitoring pharmacologic effects of new drugs or biologics, and clinical and regulatory personnel responsible for commercializing products.

CLSI has also published a new document, **Detection of HLA-Specific Alloantibody by Flow Cytometry and Solid Phase Assays; Approved Guideline (I/LA29-A)**, which describes criteria for optimizing flow cytometry crossmatching and the detection of human leukocyte antigen (HLA) alloantibody by solid-phase methods in conventional and multiplex platforms.

The specific areas addressed in the guideline include:

– technical consideration for instrument setup and staining procedures;
– screening methods;
– single-antigen and multiantigen approaches;
– reporting formats;
– clinical interpretation; and
– multicenter quality assurance.

The guideline is intended for solid organ and stem cell transplant laboratories, manufacturers of systems for histocompatability testing, and organizations that manage organ sharing.

Contact: http://www.clsi.org

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