Stem Cell Research

Current Articles

2010 - 2011

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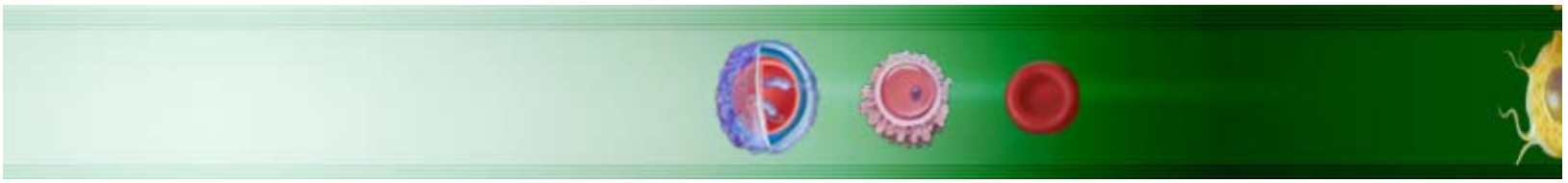


Stem Cell Research

2011 Articles

Benedict endorses adult stem-cell research as respecting human life

Catholic Online (www.catholic.org)

CASTEL GANDOLFO, Italy (Catholic Online) – Pope Benedict XVI endorsed adult stem-cell research, urging Catholic scientific institutions to increase their efforts and establish closer working relationships with others in the field to promote breakthroughs that can relieve needless human suffering.

Speaking Sept. 16 at his summer residence here to participants at an international congress, the pope said that the Catholic Church favors advanced biological research just as it has throughout its history.

“Stems Cells: What Future for Therapy?” was the theme of the Sept. 14-16 congress sponsored by the Pontifical Academy for Life and the International Federation of Catholic Medical Associations that brought together researchers and Catholic life officials at the Augustinianum Institute in Rome.

“In the face of the frequent and unjust accusations of insensitivity directed against the church," he added, "I would like to underline the constant support she has given over the course of her two 2,000-year history to research aimed at the cure of illnesses and at the good of humanity.”

Yet, Pope Benedict stressed that the church draws a distinct ethical line against research that fails to respect the dignity of the human person and does not heed the “church's constant call for full respect for human beings from the moment of conception.”

“If there has been – and there still is – resistance, it was and is against those forms of research that involve the planned suppression of human beings who are already alive, though they may not yet have been born," the pope said.

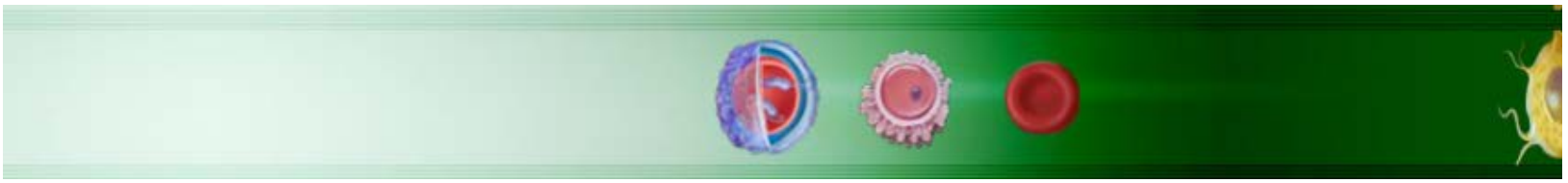
History, he said, “has condemned such science in the past, and will condemn it in the future, not only because it is devoid of the light of God, but also because it is devoid of humanity."

"In the face of the direct suppression of human beings," he continued, "there can be no compromise or prevarication; it is inconceivable for a society to fight crime effectively when it itself legalizes crime in the field of nascent life."

“A good end" of medical breakthroughs by using embryonic stem cells, he said, "can never justify intrinsically illicit means." Promising horizons are being opened through the use of adult stem cells in the cure of illnesses involving "the degeneration of tissues with consequent risks of invalidity and death for those affected," the pope said.

“Research into somatic stem cells merits approval and encouragement when it brings together scientific knowledge, the most advanced technology in the field of biology, and the ethic that postulates respect for human beings at every stage of their existence," he said.

Adult stem cells are more accurately called somatic stem cells, as they need not come from adults but can also come from children or umbilical cords, and do not require the destruction of embryonic human life.



The pope encouraged those working in Catholic scientific institutions to increase somatic stem cell research and "to establish closer contact among themselves and with others who seek, using appropriate methods, to relieve human suffering."

He praised the congress participants' commitment to and hope of "achieving new therapeutic results by using cells from the adult body without having to suppress newly-conceived human beings."

Speaking at the conference on the previous day, Sept. 15, an official of the U.S. Conference of Catholic Bishops said that embryonic stem cell research continues to pose the ethical problem of destroying human embryos, but increasingly poses the ethical problem of deceiving the public as well.

Richard M. Doerflinger, interim executive director of the U.S. bishops' Secretariat for Pro-Life Activities, said the recent scandal involving Dr. Robert Lanza of Advanced Cell Technology, who claimed he had obtained stem cells from human embryos without harming them, is "the latest in a series of deceptions" by those promoting embryonic stem cells.

"Many speeches, news stories and advertisements have declared that these cells offer a cure for Alzheimer's disease – despite the nearly universal scientific consensus that they do not," he said. "One expert at the National Institutes of Health explained this discrepancy between political message and scientific fact by commenting: 'To start with, people need a fairy tale.'"

"In fact," Doerflinger said, "we do not need a fairy tale. We need the truth. But a fairy tale is what we are sometimes getting – not only from politicians and entrepreneurs but from respected scientific journals. This must change, or science itself will lose credibility."

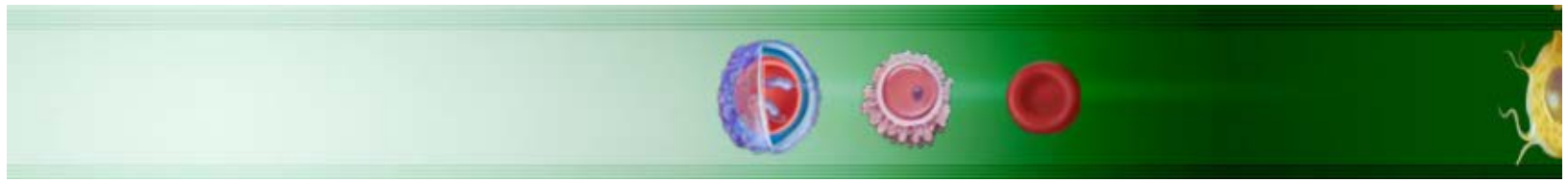
Vatican hosts adult stem cell conference:
An international conference opens in Rome Wednesday devoted to medical applications of adult stem cells.
"We see tremendous potential in these cells," says Vatican spokesman Tomasz Trafny, in a phone interview.

The Vatican Pontifical Council had earlier announced a 5-year, $1 million partnership with adult stem cell biopharmaceutical firm NeoStem and its educational foundation to research adult stem cells, examine their use and promote the cells as medical treatments.

The U.S. Council of Catholic Bishops has been a prominent critic of embryonic stem cell research in the United States. The Vatican conference will feature well-known critics of embryonic stem cell research, such as David Prentice of Catholic University in Washington, D.C., as well as accomplished stem cell researchers such as Harvard's Konrad Hochedlinger, according to its program.

Hochedlinger and colleagues have shown the potential for adult "induced" stem cells to display properties associated with embryonic stem cells and some discussions at the conference will look at such cells, Trafny says. NeoStem announced it would pursue a Phase II clinical trial of an adult stem cell treatment for heart attack patients earlier this year.

Scientists Use Human Eggs to Reprogram Skin Cells and Generate Human Pluripotent Cells:
Human somatic cell nuclear transfer (SCNT) has not yet been accomplished. SCNT involves combining an enucleated (nucleus removed) egg with the nucleus of a somatic cell (a body cell other than an egg or sperm) and stimulating the resulting embryo-like entity to divide. In humans, however, the embryo-like entity fails to reach the blastocyst stage, and so scientists are unable to derive human embryonic stem cells (hESCs) from it. Scientists in New York decided to add the somatic cell nucleus to a human egg and stimulate division without removing the



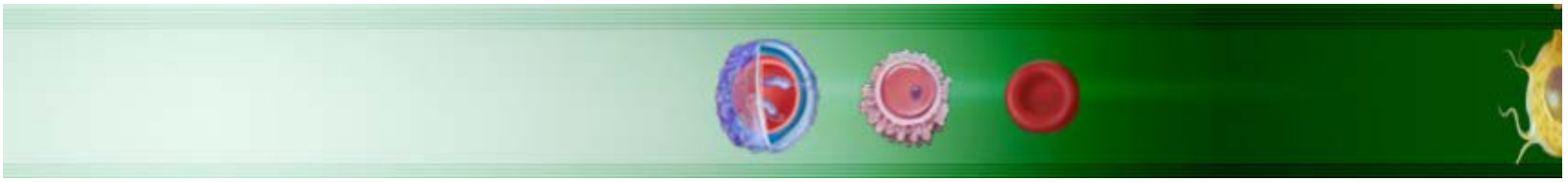
egg's nucleus. The resulting entity developed to the blastocyst stage, and the scientists derived pluripotent stem cells from it. This demonstrates that the human egg nucleus is able to reprogram the somatic cell nucleus to a pluripotent state. The new cells are triploid (contain 3 copies of the DNA, rather than the normal 2 copies) and so are unsuitable for transplantation therapy. Still, they will be a valuable resource for stem cell research. Scientists may now compare pluripotent stem cells made via this new technique with those generated via forced expression of reprogramming factors (called induced pluripotent stem cells, or iPSCs). Knowledge from these comparisons will help improve the efficiency of iPSC generation, thus advancing study of human cells for research and potential therapies. *Nature 478:70–5*; Laboratory of D. Egli (Funded by the New York Stem Cell Foundation). 2011 Oct 5.

The Ideal Control: Scientists Generate Genetically Defined Stem Cells to Study Parkinson's Disease in a Dish:

Scientists are studying induced pluripotent stem cells (iPSCs) derived from individuals with diseases in order to learn how disease develops and how they might intervene to prevent or reverse the disease process. However, some diseases still pose a challenge for this type of study. For example, in some human diseases, one altered gene does not always cause the disease, and in others, the disease develops late in life. In these cases, scientists would like to compare a cell with the altered gene to a cell with a normal copy of the gene side by side. But subtle disease characteristics might show up only if the genetic background of the cells is carefully controlled. Now, scientists have used genetic engineering to generate two types of ideal control cells for comparison—other than the disease-causing gene, the cells are genetically identical. Beginning with skin cells from a patient with an inherited form of Parkinson's disease (PD), they generated PD- iPSCs. Next, they corrected the mutation in the PD-iPSCs. They coaxed both PD-iPSCs and corrected iPSCs to generate nerve cells. They can now study the characteristics of both disease-corrected and disease-carrying nerve cells from the same person. The scientists also used genetic engineering to generate two genetically-identical human embryonic stem cell (hESC) lines carrying mutations associated with two different forms of inherited PD, for comparison with the original wild type (normal) hESC cells. Using the new cell lines as tools, scientists can now make careful comparisons to learn how these mutations cause disease. This research also demonstrates the feasibility of correcting disease-causing mutations in human cells. *Cell 146:318–31*; laboratory of R. Jaenisch (NIH-supported). 2011 Jul 22.

Scientists Take Advantage of Molecular Memory to Generate Insulin-producing Cells from Human Induced Pluripotent Stem Cells:

Scientists hope to useinduced pluripotent stem cells (iPSCs) to generate cells to replace those lost or damaged by diseases such as diabetes. Individuals with diabetes can't regulate their blood sugar because their bodies don't make enough insulin, or their bodies don't respond to insulin properly. Restoring insulin-producing ability (and thus blood sugar regulation) is a major therapeutic goal. Scientists are trying to use stem cells to generate human pancreatic beta cells – the insulin-producing cells of the pancreas. Prior research suggests that even after reprogramming, iPSCs "remember" their original identities. Israeli researchers hypothesized that iPSCs generated from beta cells might also retain a molecular memory that could be exploited to generate more beta cells. They compared gene expression patterns in 3 cell types: non-beta-cell derived human iPSCs, beta-cell-derived human iPSCs (BiPSCs), and human embryonic stem cells (hESCs). Their data suggest that BiPSCs maintain an open chromosome structure (i.e., genes more likely to be expressed) in areas of the chromosome that contain genes most important for beta cell function. These important beta cell-specific regions of the chromosome were not open in either non-beta-cell-derived iPSCs or in hESCs. Next, the scientists differentiated BiPSCs and hESCs into beta cells, transplanted them into diabetic mice, and evaluated the abilities of each to regulate blood sugar. Their results suggest that BiPSC-derived beta cells matured faster after transplantation and produced higher levels of insulin than beta cells produced from hESCs. These data support previous studies' conclusions that reprogrammed cells retain an epigenetic memory of their former cell type, and suggest that scientists may be able to take advantage of this memory to generate cells for replacement therapies. *Cell Stem Cell 9:17–23*; Laboratory of N. Benvenisty (Supported by Israel and the JDRF). 2011 July 8.

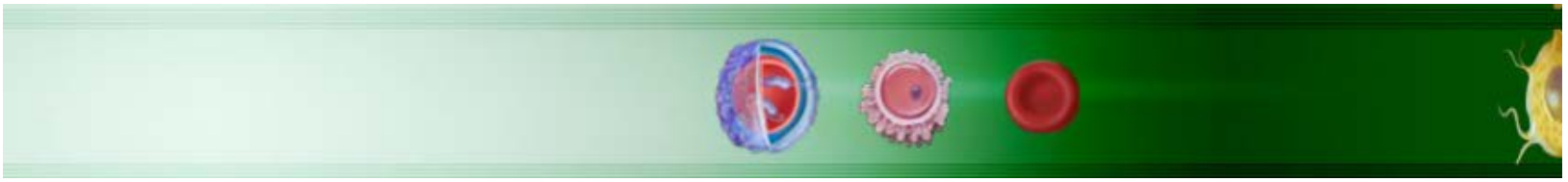


Induced Pluripotent Stem Cells Rejected in Mice:

Scientists hoped that replacement tissues derived from induced pluripotent stem cells (iPSCs) generated from adult skin cells would avoid rejection after transplantation into the original skin cell donor. This potential gave iPSCs a proposed advantage over tissues derived fromhuman embryonic stem cells. Ironically, a mouse study now demonstrates that iPSCs generated from an individual mouse are rejected even by that same mouse, while unrelated mouse ESCs are tolerated. This scenario differs from an actual transplant, because the stem cells, and not differentiated cells, were transplanted into the mice. Nonetheless, this study highlights a potential safety concern for clinical applications of iPSC-derived cells. The authors suggest that changes in gene expression during the cells' reprogramming to iPSCs may attract attack from the recipient's immune system. *Nature 474: 212–216*; laboratory of Y. Xu. (NIH and CIRM-supported). 2011 June 09.

Scientists are generating Induced Pluripotent Stem Cells (iPSCs) from individuals with a disease, and using these cells to learn more about causes and possible treatments for the diseases.

1. **Telomere shortening and loss of self-renewal in dyskeratosis congenita induced pluripotent stem cells**. Individuals who inherit dyskeratosis congenita(DC) have characteristic abnormally-shaped fingernails and toenails, a lacy rash on the face and chest, and white patches in the mouth. They also have an increased risk of developing several life-threatening conditions, including bone marrow failure, leukemia, and pulmonary fibrosis. Although patient-derived iPSCs offer hope for disease modeling, it is unclear whether the iPSCs will mirror the faulty biochemical characteristics of the patients from which they were derived. NIH-funded scientists generated iPSCs from individuals with several different forms of inherited DC, and determined that the iPSCs demonstrate the same faulty biochemistry found in the original patient cells, and that the severity of the cellular errors correlates with the patients' disease severity. This makes patient-derived iPSCs a valid model to study DC, and to screen possible treatments. *Nature* [Epub ahead of print]; laboratories of S.E. Artandi and R.A. Reijo Pera. (NIH-supported). 2011 May 22.
2. **Modelling schizophrenia using human induced pluripotent stem cells.Schizophrenia** is a chronic, severe, and disabling brain disorder that affects about 1% of Americans. Scientists generated iPSCs from individuals with schizophrenia (SCZD-iPSCs), and then differentiated these SCZD- iPSCs into nerve cells, or neurons. They compared properties of iPSC-derived neurons from individuals with and without schizophrenia to try to identify how schizophrenia affects brain function. Neurons generated from SCZD-iPSCS demonstrated differences in gene expression and cell-cell communications. When treated with an antipsychotic drug (loxapine), the neurons derived from SCZD-iPSCS behaved more like iPSC-derived neurons of individuals without schizophrenia. *Nature 473:221–5*; laboratory of F. Gage. (CIRM-supported). 2011 May 12.
3. **Genetic correction and analysis of induced pluripotent stem cells from a patient with gyrate atrophy.** Gyrate atrophy is an inherited disorder characterized by progressive vision loss. People with this disorder continually lose cells (atrophy) in the retina, which is the specialized light-sensitive tissue that lines the back of the eye, and in a nearby tissue layer called the choroid. Since scientists know which gene mutation causes this disorder, they derived iPSCs from a patient and attempted to correct the mutation. Next, they compared the original patient-derived iPSCs to the gene-corrected iPSCs to determine if the prolonged culture period used to achieve gene correction caused additional mutations in the cells. Although the process of generating patient-derived iPSCs caused numerous mutations, they determined that the correction of the genetic defect in those iPSCs did not cause new mutations.*PNAS 108: 6537–42*; laboratory of J. Thomson. (NIH-supported). 2011 April 19.
4. **Using induced pluripotent stem cells to investigate cardiac phenotypes in Timothy syndrome. Timothy syndrome** is a rare disorder that affects many parts of the body including the heart, digits (fingers and



toes), and the nervous system. Individuals with Timothy syndrome suffer from a heart condition called long QT syndrome, which causes the heart muscle to take longer than usual to recharge between beats. This abnormality in the heart's electrical system can cause irregular heartbeats (arrhythmia), which can lead to sudden death. NIH-funded scientists generated iPSCs from individuals with Timothy syndrome, anddifferentiated the iPSCs into heart cells, or cardiomyocytes. By performing tests on the iPSC-derived cardiomyocytes, they were able to identify the molecular basis for long QT syndrome. Next, they tested drugs on the cardiomyocytes and identified one, roscovitine, which seemed to correct the arrhythmia. *Nature 471:230–4*; laboratory of R. Dolmetsch. (NIH-supported: NIH Director's Pioneer Award to R. Dolmetsch). 2011 March 10 .

Discovery of Lung Stem Cells May Herald New Treatments

NIH-supported scientists have found stem cells in the human lung capable of forming different parts of the lung, including blood vessels. *NEJM 364(19)*; laboratory of P. Anversa. 2011 May 12.

Exploring Different Methods to Make Induced Pluripotent Stem Cells:

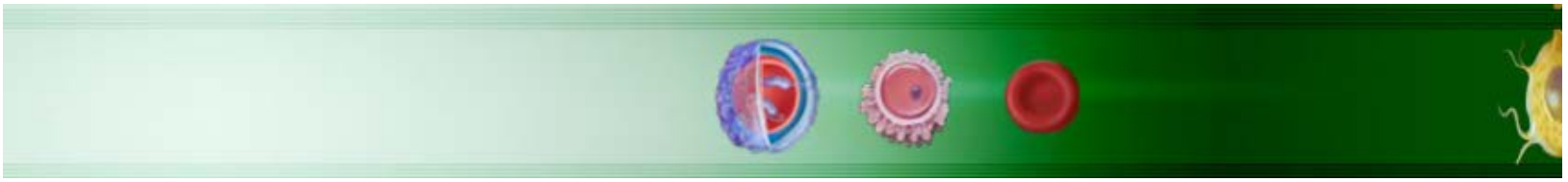
Certain aspects of the original induced pluripotent stem cell (iPSC) reprogramming technique are not suited for possible clinical applications. See "Safer Reprogramming of Human Cells." Scientists continue to develop improved methods for generating iPSCs.

1. **Use of miRNA**: Scientists identified microRNA (miRNA) that was highly expressed in embryonic stem cells, and tested its ability to reprogram non-embryonic mouse and human fibroblasts. The miRNA reprogrammed non-embryonic cells without the use of any viruses, or any of the traditional reprogramming factors (Oct4/Sox2/ Klf4/Myc, or OSKM) and was two orders of magnitude more efficient than the OSKM methods. *Cell Stem Cell 8: 376–388*; laboratories of J. A. Epstein and E.E. Morrisey (NIH-supported). 2011 April 8.
2. **Beginning with Cells that are Amenable to Reprogramming:** Characteristics of certain cell types, when used as starting material, are likely to make them more amenable to being reprogrammed into iPSCs. Scientists determined thatepigenetic and gene expression in cord blood and adult mononuclear (blood) cells were closest to iPSCs and hESCs. They reprogrammed these two cell types using a non-integrating vector (does not insert itself into the DNA of the cells) carrying 5 reprogramming factors. The technique takes less time than reprogramming other cell types, such as fibroblasts (<10 days vs. 4+weeks), and they were unable to detect any leftover vector in the resulting iPSCs. *Cell Res. 21: 518–529*; laboratory of Linzhao Cheng (NIH-supported). 2011 March.

How to Make More Stem Cells:

Scientists know that stem cells are found in small quantities and in particular locations within many (if not all) organs of the human body. Although these resident stem cells are able to replace cells of the organ following normal wear and tear, they do not seem able to repair or correct more severe organ damage—like that caused by disease or severe injury. Scientists hypothesize that the limited number of adult stem cells and their limited ability to make more copies of themselves (a process known as self-renewal) may be at fault. They tried to overcome this problem by isolating human neural stem cells and forcing them to self-renew. To do this, they infected the neural stem cells with a virus carrying v-myc, a factor known to be important for self-renewal. V-myc was combined with a tetracycline regulation system, so as to activate self-renewal of the cells only when the drug tetracycline was added to the culture system. The scientists used this system to generate large numbers of neural stem cells. Next, the human neural stem cells were transplanted into a mouse model of human stroke.

The study reports three important observations after the transplant:



1. self-renewal stopped because there was no longer any tetracycline in the system,
2. some of the transplanted cells survived, migrated to the area of injury, and differentiated into neurons and glia, and
3. the mice demonstrated improvement of stroke symptoms.

The authors propose this new system as a means of generating large numbers of therapeutic cells for a particular organ. *Proc Natl Acad Sci U S A. 108:4876–81*; Laboratories of S.U. Kim and E. Snyder (Not NIH-supported). 2011 March 22.

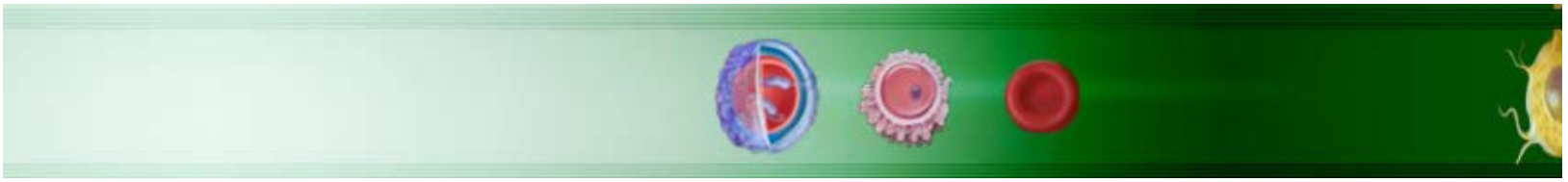
2010 Articles

An Improved Mouse Model for Human Duchenne Muscular Dystrophy:

Individuals with Duchenne muscular dystrophy (DMD) have a mutation in the gene that makes a muscle protein called dystrophin. Dystrophin is a critical component of muscle cell membranes, and faulty dystrophin causes the muscle cells to become damaged when they are under stress. Individuals with DMD suffer a gradual loss of control of the skeletal muscles used for voluntary movements. Scientists generated mice with faulty dystrophin to serve as an animal model to study the effects and progression of DMD. However, the DMD mice do not develop symptoms as severe as seen in human DMD, demonstrating only mild muscle weakness and a robust ability to regenerate muscle fibers. Since the mice have faulty dystrophin, NIH-funded investigators hypothesized that the DMD mice fared better due to hardier muscle stem cells (MuSCs), which are able to divide and replace muscle damaged by the faulty dystrophin. They believed mouse stem cells are hardier because the ends of the chromosomes within each mouse cell are protected from damage caused by constant cell division by long "caps" on their ends, called telomeres. An enzyme called telomerase is responsible for maintaining each cell's telomeres. When the scientists generated mice with both faulty dystrophin and faulty telomerase, the mice demonstrated progressive muscle wasting, as seen in human DMD. Their results suggest that human DMD is caused by a combination of the continued need to repair damaged muscle and exhaustion of the MuSCs. This improved mouse model of DMD provides new insight into the causes of human DMD, and will help scientists test drugs to treat its symptoms. *Cell* 143:1059–1071; laboratory of H.M. Blau (NIH-funded). 2010 December 23.

Scientists Convert Human Skin Cells Directly to Blood Stem Cells:

In direct reprogramming (also called direct conversion), scientists use what they know about early development of a cell type to change the identity of a mature cell to resemble that of another cell type. The process differs from the generation of induced pluripotent stem cells (iPSCs) because the directly reprogrammed cells are not taken all the way back to an undifferentiated state, but are instead taken from one mature state to another. Canadian scientists grew human skin cells (fibroblasts) in culture with the addition of specific transcription factors (proteins found within cells that regulate a gene's activity) known to be important for generating blood stem cells. These culture conditions enabled them to generate a blood stem cell that could be manipulated in culture to produce all of the blood cell types. The scientists hope their results will enable them to make enough patient-specific cells for therapies, without the complications that arise if the starting materials are human pluripotent stem cells. *Nature* 468:521–6; laboratory of M. Bhatia (non-NIH supported). 2010 November 25.



Scientists Model Autism and Test Potential Treatments Using Human Induced Pluripotent Stem Cells:

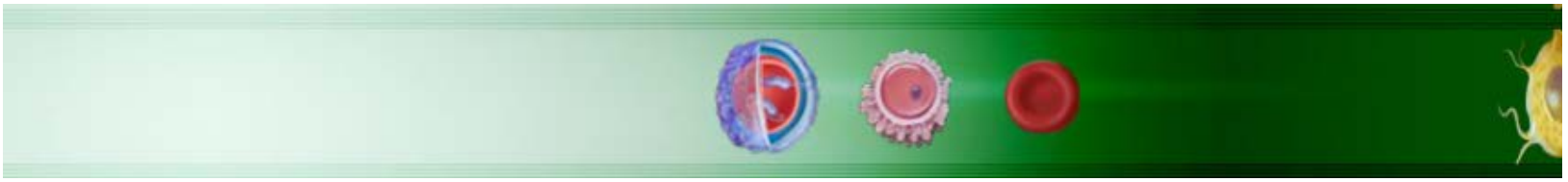
Rett Syndrome (RTT) is a disorder that impacts the developing nervous system and affects girls almost exclusively. RTT is considered to be an autism spectrum disorder, and girls with RTT often exhibit autistic-like behaviors in the early stages. Although scientists determined that a defective gene causes RTT, they could not easily study nerve cells from girls with RTT to understand why or how RTT causes its negative effects on the nervous system. Recently, NIH-supported scientists used skin cells from individuals with and without RTT to generate induced pluripotent stem cells (iPSCs). Next, they used the iPSCs to generate nerve cells (neurons). Compared to iPSC-derived neurons from unaffected individuals, RTT-iPSC-derived neurons made fewer physical connections (synapses) with neighboring neurons, were smaller, and were not as effective at communicating with other neurons. The scientists tested two drugs that improve RTT when given to a mouse model of RTT (IGF1 and gentamycin) and found that they also improved the function of human RTT-iPSC-derived neurons. This research demonstrates that RTT-iPSC-derived neurons are valuable tools to study disease mechanisms and to test potential treatments for RTT and other autism spectrum disorders. *Cell* 143:527–39; laboratory of A.R. Muotri (Supported by NIH Director's New Innovator Award Program). 2010 November 12.

RNA Provides a New Way to Achieve Efficient Reprogramming of Human Cells:

Scientists are constantly trying to improve both the efficiency and the safety of the methods for generating induced pluripotent stem cells, or iPSCs. Massachusetts-based scientists now report that they have developed a new reprogramming method that uses RNA to coax cells to make 4 transcription factor proteins critical for the reprogramming process. The method reprograms more cells in less time: It's 2 orders of magnitude more efficient than current methods, and the whole process takes a little more than 2 weeks, rather than the standard month. The method is also safer, because the RNA that reprograms the cells degrades, eliminating the possibility that it could interfere with cell function. Once they generated iPSCs, the scientists adapted the same RNA method to coax the iPSCs to differentiate into muscle cells by inserting RNA that codes for an important muscle gene. This new method may now enable efficient generation of stem cells and differentiated cells for use in regenerative medicine, cell-based therapies, and to test potential therapeutic drugs.*Cell Stem Cell* 7: 1–13 (2.5MB PDF; get Adobe Reader) [early online version]; laboratory of D.J. Rossi (NIH-supported). 2010 November 5.

Chromosomes of Induced Pluripotent Stem Cells Not Stable in Culture:

Since they are derived from adult body cells, such as skin cells, induced pluripotent stem cells (iPSCs) were thought to have normal chromosomes. However, scientists in Israel have now determined that human iPSCs also have chromosome abnormalities, similar to those seen in human embryonic stem cells (hESCs). Further examination of the cells suggested that some of the iPSCs' chromosomal abnormalities arise as a result of the reprogramming process itself, some are due to adaptations that developed during a long period of time in culture, and others originate from an abnormality in the original adult cell. A common abnormality in the human iPSCs is trisomy 12—the presence of 3 rather than the normal 2 copies of chromosome 12, which is important for controlling cell division. This chromosome abnormality is also common in cultured hESCs. Since loss of control of cell division causes cancer, these data demonstrate that tissues derived from both iPSCs and hESCs must undergo careful chromosomal analysis prior to transplantation in order to ensure their safety.*Cell Stem Cell 7:521-31*; laboratory of N. Benvenisty (supported by Israel). 2010 October 8.



Female Human Induced Pluripotent Stem Cells (iPSCs) Retain an Inactive X Chromosome:

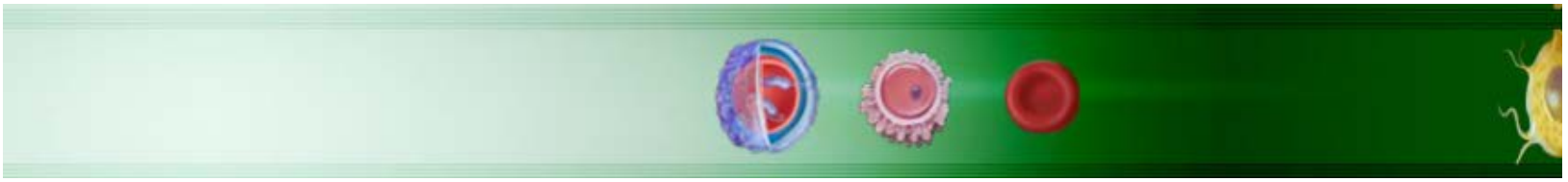
During normal female development, one X chromosome in each cell's nucleus is inactivated. Stem cells, however, are different. Female mouse embryonic stem cells (mESCs) have two active X chromosomes, but many female human ESCs have already inactivated one X chromosome (see Deriving Human Embryonic Stem Cells under Low Oxygen Concentrations Produces Stem Cells with Two Active X Chromosomes). Next, scientists considered the activation state of X chromosomes in iPSCs. During reprogramming of female mouse skin cells, the previously inactivated X chromosome is reactivated. Is the same true in humans? No—scientists determined that human iPSCs generated from human female skin cells under standard culture conditions carry an inactivated X chromosome. In addition, although human female skin cells randomly inactivate either the mother's X chromosome or the father's X chromosome, the iPSCs derived from them are all identical in their X chromosome activation status. Each female human iPSC inactivates the X that was inactivated in the original female skin cell from which it was generated. This information will have important implications for the clinical use and disease modeling using female human iPSCs. The authors also suggest it will be useful to exploit X chromosome inactivation status for treatment of X-linked diseases. *Cell Stem Cell* 7:329–342; laboratory of K. Plath (NIH-supported). K. Plath holds an NIH Director's Young Innovator Award. 2010 September 3.

Imitating Muscle Cells' Natural Environment Helps them to Flourish in Culture:

Although it is well established that mature muscles contain muscle stem cells (MuSCs) that maintain and repair muscle, scientists have been unable to grow large numbers of MuSCs in laboratory culture. NIH-supported scientists used a mouse model to test the hypothesis that growing the cells under conditions that imitate the physical properties of the muscle, where MuSCs are found in nature, may enable the growth of MuSCs in the laboratory. Instead of using the standard rigid (stiff) plastic tissue culture dishes, they grew mouse MuSCs on a less-rigid gel with physical properties similar to mouse muscle. MuSCs grown on a mouse muscle-like gel medium were compared to MuSCs grown on standard plastic tissue culture dishes that had been coated with a thin layer of gel. This comparison enabled them to sort possible chemical effects of the gel from the effects of the rigidity of the gel. MuSCs grown on gel outperformed MuSCs grown on gel-coated plates on several measures: survival, cell division, maintenance of stem cell–like properties, and post-transplantation survival and homing to a damaged muscle. This research highlights another important aspect of stem cell maintenance and differentiation: physical properties of the culture conditions. Combined with knowledge of biochemical signals, this work brings us one step closer to developing cell-based therapies. *Science*329:1078–81; laboratory of H. Blau (NIH-supported).
2010 August 27.

Hope for Parkinson's Disease—Human Dopamine-Producing Neurons from Induced Pluripotent Stem Cells:

Scientists hope to use induced pluripotent stem cells (iPSCs) to generate replacements for cells affected by disease. Parkinson's Disease (PD) is a degenerative disorder of the central nervous system caused by the loss of dopamine-producing brain cells (dopaminergic neurons), and replacement of these neurons is a major therapeutic goal. Scientists have now adapted a defined, xeno-free (no animal products) culturing technique previously developed to generate dopaminergic neurons from human embryonic stem cells (hESCs) for use on iPSCs. The iPSCs differentiated to produce neural stem cells and then dopaminergic neurons in a manner similar to hESCs. Mature iPSC-derived dopaminergic neurons survived after being transplanted into rats that suffer a PD-like condition, and the rats' behavior improved. The scientists compared dopaminergic neurons derived from hESCs to those derived from iPSCs, and found that both shared similar gene expression profiles overall, with some differences. Scientists have not yet determined whether these differences will affect which type of stem cell is best for use in PD therapies. This xeno-free culture technique brings iPSC-derived therapies one



step closer to clinical use. *Stem Cells* [Epub ahead of print]; laboratory of X. Zeng (NIH-supported). 2010 August 16.

Scientists Use Defined Factors to Directly Reprogram Mature Mouse Cells into Heart Muscle Cells

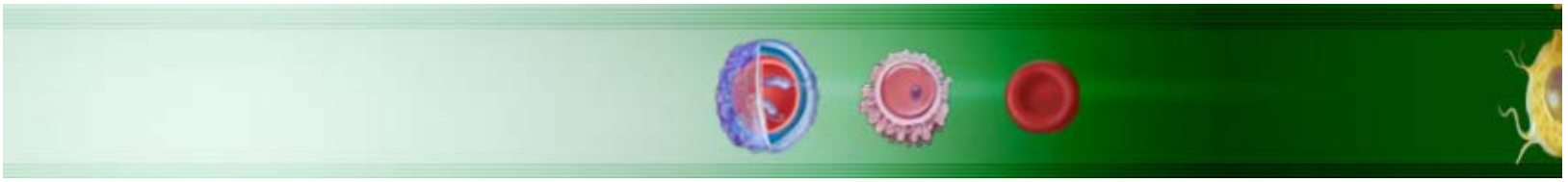
Scientists have begun to use what they know about genes expressed during normal development to directly reprogram adult cells. Direct reprogramming switches the identity of a mature cell without taking it all the way back to a primitive state. Scientists now report that the use of a combination of three transcription factors(Gata4, Mef2c, and Tbx5) whose genes are active during early development was able to reprogram postnatal mouse heart or skin fibroblasts directly into differentiatedheart muscle–like (cardiomyocyte-like) cells. These reprogrammed cells expressed both markers and genes characteristic of cardiomyocytes and contracted (beat) like cardiomyocytes. Scientists now hope to use this technique on human cells to generate cardiomyocytes for treatment of heart damage or heart disease. *Cell* 142: 375–386; laboratory of D. Srivastava (NIH-supported). 2010 August 6.

Induced Pluripotent Stem Cells Remember their Origins:

Scientists hope to use tissue-matched stem cells to treat human diseases. They are continuing to explore whether induced pluripotent stem cells (iPSCs) are truly pluripotent "blank slates", ashuman embryonic stem cells (hESCs) are thought to be, or whether they maintain some characteristics of their tissues of origin. Two recent reports suggest that although cells from different tissue sources can be reprogrammed into iPSCs, they also retain a bias towards differentiation into the tissue type from which they originated. For example, a blood cell retains molecular markers of its identity as a blood cell, and differentiates more readily into a blood cell as opposed to another cell type, such as bone. The bias seen in the iPSCs can be "undone" with drug treatment, by differentiating the cells into the particular cell type of interest and then reprogramming them for a second time, or by extended culturing. Scientists with an understanding of the molecular "starting points" of iPSCs can use this knowledge to help them more easily generate a specific cell type. Understanding the cells' biases will also be important as scientists use iPSCs to model human diseases. *Nature* [Epub ahead of print]; laboratory of G.Q. Daley (NIH-supported). 19 July 2010. *Nat. Biotech*[Epub ahead of print]; laboratory of K. Hochedlinger (NIH-supported). 2010 July 18.

Safe Stem Cell-Derived Tissue Used to Treat Spinal Cord Injury:

Patients treated with cells or tissues derived from pluripotent stem cells risk the possibility that the transplant also contains one or more undifferentiated cells, thus increasing the recipient's risk for tumors. Using mice, Japanese scientists developed a method (Miura *et al.*, Nat. Bio. 27: 743–5, 2009) to evaluate the likelihood of tumor formation in primitive neural tissues called neurospheres. The neurospheres were generated from induced pluripotent stem cells (iPSCs). Neurosphere safety was tested by transplanting them into the brains of mice with compromised immune systems, whose bodies are not able to destroy tumors as readily as normal mice. Transplanted neurospheres were called "tumorigenic" if they produced a type of tumor called ateratoma after transplantation, and "non-tumorigenic" if they did not form a teratoma. Neurospheres pre-evaluated as non-tumorigenic improved movement abilities when subsequently used to treat spinal cord-injured mice, and did not form teratomas within the 6-week observation period. The transplanted tissue generated all major spinal cord cell types, and helped cover the spinal cord in an insulatingmyelin sheath. In contrast, mice treated with neurospheres pre-evaluated as tumorigenic temporarily improved in mobility but lost this improvement as the neurospheres formed teratomas within 6 weeks. This research confirms the reported evaluation method as a valuable tool for predicting the safety of tissues destined for use in transplantation. It also provides hope that iPSC-derived neurospheres may one day be used to treat humans



with spinal cord injuries. *Proc Natl Acad Sci U S A* [Epub ahead of print]; laboratory of S. Yamanaka and H. Okano (funded by Japan). 2010 July 13.

Reprogramming Human Cells under Mouse Embryonic Stem Cell Culture Conditions Makes Them Easier to Manipulate:

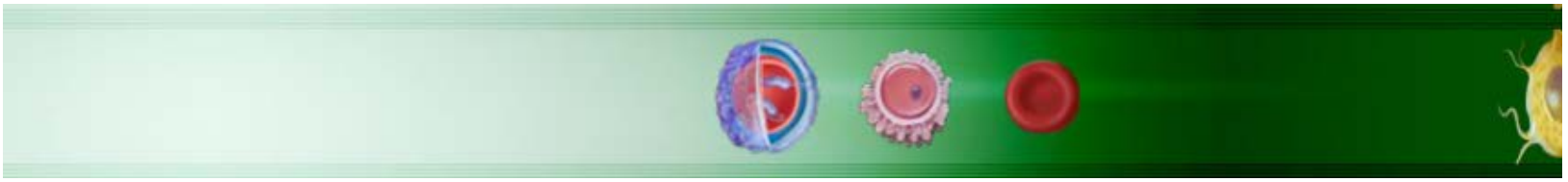
Scientists have nearly 3 decades of experience with mouse embryonic stem cells (mESCs), which are used to generateknockout mice to study gene function. However, human embryonic stem cells (hESCs) are not as easy to manipulate as mESCs—they're highly resistant to gene targeting via homologous recombination and require special handling and culturing conditions. Scientists would like to be able to grow and manipulate human stem cells with the ease of mESCs. Now, scientists report that reprogramming human cells to beinduced pluripotent stem cells (iPSCs) in the presence of a factor required for mESC culture (called LIF) makes the human iPSCs behave more like mESCs. The technique requires temporary expression of 5, rather than the more standard 4 reprogramming factors. Human iPSCs generated under these conditions grow in colonies shaped like those of mESCs, and are more easily manipulated for gene targeting studies—making them a valuable tool for research. *Cell Stem Cell 6(6): 535–46*; laboratory of N. Geijsen (NIH-supported). 2010 June 4.

Successfully-Reprogrammed Cells Can be Identified by Sight:

Reprogramming of cells into induced pluripotent stem cells (iPSCs) is inefficient—only about 1% of cells in the culture dish are successfully reprogrammed into iPSCs. Thus, measuring visible changes that occur during iPSC reprogramming is not accurate if measurements are averaged across all the cells in a dish. Scientists have now developed an imaging system to watch single mouse fibroblasts as they are reprogrammed. They fluorescently labeled mouse embryonic fibroblasts (MEFs) and "seeded" them into dishes of unlabelled MEFs. The scientists then subjected the cultured MEFs to an iPSC- reprogramming protocol and collected time-lapse images of labeled cells during 12- to 14-day long experiments. At the end of the experiments, labeled cells were scored for characteristics of reprogrammed cells. The scientists then traced reprogrammed cells back in time through the recorded images of the labeled cells. They determined that successful reprogramming could be identified visually because these cells changed their size and shape and began dividing rapidly soon after they were treated with the iPSC-reprogramming protocol. Their analyses determined that cells are likely to be reprogrammed in a series of sequential and progressive steps. This research is helping scientists learn more about how and when cells are reprogrammed, and may enable safer and more efficient generation of iPSCs for regenerative medicine. *Nature Biotech 28(5): 521–7*; laboratory of A. Meissner (author A. Regev is supported by an NIH Pioneer Award). 2010 May.

Deriving Human Embryonic Stem Cells under Low Oxygen Concentrations Produces Stem Cells with Two Active X Chromosomes:

The human X chromosome contains over 1,000 genes that are vital for development and cell survival. However, because females carry two copies of the X chromosome, they could suffer negative consequences if they produce a double dose of X-linked genes. To correct this imbalance, female mammals silence one of their two X's. X chromosome inactivation represents a maturation process, and makes X-inactivated stem cells potentially less pluripotent than stem cells with two active X chromosomes. In mouse embryonic stem cells (mESCs), both X chromosomes of a female-derived line are active. Human embryonic stem cells (hESCs), however, are thought to be developmentally "older" than mESCs because one X chromosome is typically already inactivated in female-derived lines. The hESCs' inactivated X chromosome is believed to be responsible for at least some of the differences between mESCs and hESCs. Scientists decided to derive hESCs under the type of low oxygen conditions that they would experience within the embryo, to determine if this would affect their X chromosome activation status. Their data suggest that low oxygen is indeed critical. In low oxygen,



derived hESCs have 2 active X chromosomes, and in high oxygen (such as is found in atmospheric conditions), one X chromosome is irreversibly inactivated. Oxygen concentration seems to directly affect whether the gene whose protein product inactivates the X chromosome (called *XIST*) is produced—in low oxygen conditions, the *XIST* gene is blocked, and in high oxygen conditions, it is activated. This information about how the culture environment affects stem cells is critical as scientists work to use both hESCs andinduced pluripotent stem cells (iPSCs) to develop therapies for treating human diseases. *Cell 141:872–83*; laboratories of R. Jaenisch and M. Mitalipova (privately funded). 2010 May 28.

Scientists develop a protocol to generate hair cell-like cells from embryonic and induced pluripotent stem cells:

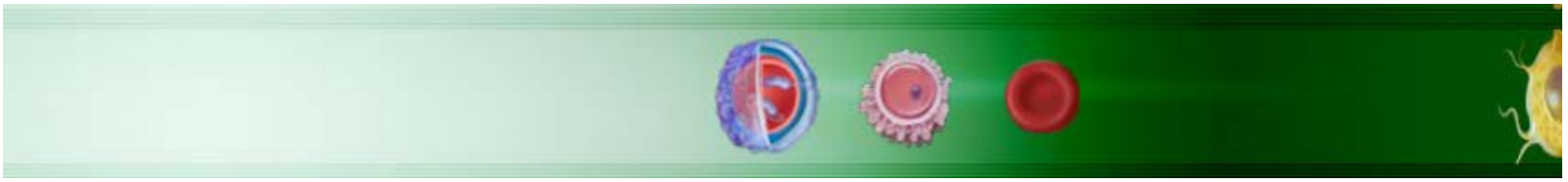
Hair cells in the inner ear are critical for both hearing and balance. Unfortunately, mammals don't normally regenerate hair cells that are damaged or destroyed, and loss of hair cells leads to loss of hearing or balance. In addition, scientists have had trouble gathering enough of these rare cells to study them in the laboratory. Now, NIH-funded scientists have developed a protocol for generating hair cells from both mouse embryonic stem cells and mouseinduced pluripotent stem cells (iPSCs). Tests suggest that the cells behave like hair cells in response to mechanical stimulation. This protocol will now help scientists generate large numbers of hair cell-like cells to study in the laboratory. Scientists hope these mouse studies will teach them enough to enable them to generate similar hair cell-like cells from human stem cells. If scientists can understand the molecular events that enable hair cells to organize properly within the ear and send messages to the brain, they may be able to restore hearing and balance to those who have lost these abilities after hair cell damage or death. *Cell 141:704–16*; laboratory of S. Heller (NIH-supported). 2010 May 14.

Gene silencing may limit iPSC potential:

Research suggests that iPSCs may have more limited potential than ESCs. To determine the reason, NIH-funded investigators compared mouse ESCs to mouse iPSCs from an identical genetic background. They discovered that a section of chromosome 12, containing genes vital to fetal development, was inactivated, or "turned off" in most iPSCs. The few iPSC lines that did not show inactivation of this section demonstrated a greater potential fordifferentiation, including being able to produce live mice using a tetraploid complementation assay. If scientists can understand why and how the current method of reprogramming silences these genes, they may be able to develop improved methods for reprogramming cells into iPSCs. *Nature 465(7295):175–81*; laboratory of K. Hochedlinger (NIH-supported). 2010 May 13.

New Culture Technique Helps Select for Adult Human Cells that Demonstrate Multipotency:

Under normal conditions, adult stem cells are activated to repair injuries after the body is exposed to stress, such as disease or injury. Japanese scientists mimicked this stress by adding an enzyme called trypsin to the culture medium of human bone marrow stromal cells or fibroblasts. This caused some of the cells to clump up and, after being cultured in suspension, they began to express genes typically expressed by human embryonic stem cells, such as Nanog, Oct3/4, SSEA-3, and Sox-2. Cell division stopped after 2 weeks, but resumed after the cells were again grown in adherent culture conditions. In order to continue expanding the number of cells, the scientists grew them in cycles of culture in first adherent and then suspension conditions. These cells, named Muse (for **MU**ltilineage differentiating**S**tress **E**nduring,) do not divide as actively as other stem cells and do not formteratomas in immunodeficient mice. However, single Muse cells are able to form derivatives of all 3 germ layers, both *in vitro* and *in vivo*. This cyclical culturing technique will help scientists enrich and expand existing adult stem cells from accessible sources such as bone marrow or cell banks, without the need to introduce genes, as is done to generate induced Pluripotent Stem Cells (iPSCs). *PNAS: 107(19):8639–43*; laboratory of M. Dezawa (privately funded in Japan). 2010 May 11.

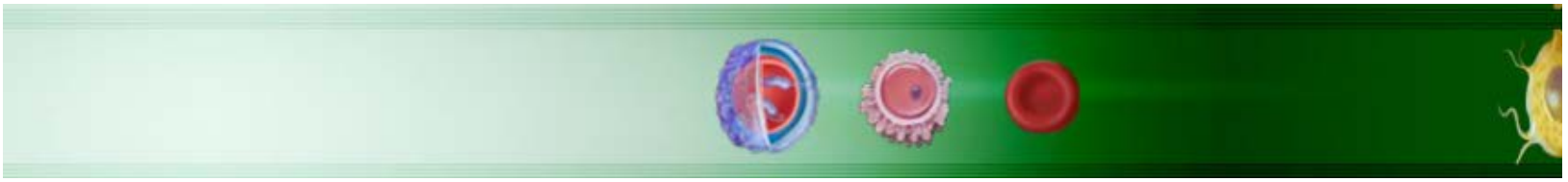


Bone stem cell niche identified:
NIH scientists have identified the location and signaling pathways necessary for proliferation and maintenance of bone stromal cells (BSCs), the stem cells that give rise to mature bone. A mouse model lacking one copy of the gene that forms part of protein kinase A, or PKA, was prone to developing various tumors, including tail bone lesions. When researchers removed a second part of the PKA protein, the bone abnormalities were more widespread and occurred in younger animals. In examining the lesions, scientists identified a population of BSCs in adult animals, which they termed aBSCs, present at locations where bone is actively growing, such as under the growth plate of long bones and vertebrae. The population also expressed proteins known to be expressed in other stem cell populations. By understanding both the signaling pathways that lead to BSC proliferation and the necessary supporting structures for such growth, researchers are moving closer to successfully growing bone tissues outside the body, potentially leading to replacement of diseased or damaged bone in the future. *PNAS 107(19):8683–8*; laboratories of C. Stratakis (NICHD) and P. Robey (NIDCR) (supported by the NIH Intramural Program). 2010 May 11.

Modeling Fragile X Syndrome—Human Embryonic Stem Cells and Induced Pluripotent Stem Cells are Different:
Scientists hope that studies of stem cells that carry human diseases will help them understand and treat the diseases. In an inherited genetic condition called Fragile X Syndrome, there is a change, or mutation, in a single gene called the Fragile X Mental Retardation 1 (FMR1) gene. This gene normally makes a protein that the brain needs in order to develop properly. The Fragile X mutation to the FMR1 gene causes the body to make only a little bit or none of the protein, which causes the symptoms of Fragile X. Scientists have generated stem cell lines from human embryos that carry a Fragile X mutation. Tests showed that although the FMR1 gene is expressed normally in these Fragile X human embryonic stem cells (hESCs), it is silenced (turned off) after the cells begin todifferentiate. Now, scientists have generated induced pluripotent stem cells (iPSCs) from individuals with Fragile X. Tests on these cells indicated that the FMR1 gene is silenced even in the reprogrammed iPSCs. These studies demonstrate important differences in stem cells from the two sources (hESCS vs. iPSCs), which must be considered as scientists use them to study diseases and disorders. *Cell Stem Cell 6: 407–411*; laboratories of G.Q. Daley and N. Benvenisty (NIH-supported). 2010 May 7.

Regenerating Teeth by Providing a Scaffold:
Scientists would like to regenerate human teeth lost to accidents and decay. Since transplanted tooth stem cells are not currently useful for tooth regeneration, scientists tested whether they could generate teeth in rats by providing a scaffold that the native (endogenous) stem cells could colonize. After 9 weeks, rats that received implanted scaffolds showed evidence of new bone and ligament formation that would support a tooth. In those rats that received both scaffolds and treatment with growth factors such as BMP7, the scientists observed more endogenous stem cells on the scaffold, and the developing tooth-like structure had a more vigorous blood supply. This method may one day enable scientists to use scaffolds in humans to generate biological bone and ligaments (roots) to support implanted crowns to replace lost or damaged teeth. *J. Dental Res. published online May 6, 2010*; laboratory of J. Mao (NIH-supported). 2010 May 6.

Small molecules Ease Culture of Human Embryonic Stem Cells (hESCs):
hESCs are notoriously difficult to grow and maintain in culture, requiring substantial knowledge, training, and experience. In order to improve this process, privately-funded scientists have been examining ways to modify hESC culture conditions to help the cells grow more easily. They used high-throughput chemical screening to identify two small molecules, Thiazovivin (Tzv) and Pyrintegrin (Ptn), which promote hESC growth and survival

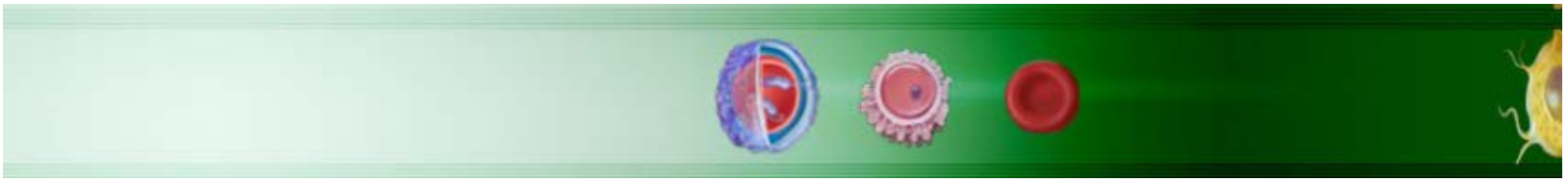


by enhancing cell adhesion. These results emphasize the importance of the microenvironment for hESC survival and self-renewal. This study will help scientists maintain hESC cultures with less effort and resources. *Proc Natl Acad Sci U S A. 107(18): 8129–8134, 2010*; laboratory of S. Ding (privately funded). 2010 May 4.

Derivation, Propagation and controlled differentiation of hESCs in suspension:
Traditionally, hESCs are derived, expanded, and differentiated as adherent colonies on either feeder layers or extracellular matrix (ECM) proteins, because propagation as free-floating clusters is thought to induce differentiation. In this study, scientists altered the culture medium, adding several factors known to promote continued propagation without differentiation, including ECM proteins, neurotrophic factors, FGF2 and activin. They confirmed that hESCs grown free-floating in the new medium remained undifferentiated, were usually genetically stable, and retained their ability form teratomas or differentiate into all 3 germ layers *in vitro*. The novel culture medium also supported the derivation of 3 new hESC lines, either from the inner cell mass of a blastocyst stage embryo, or directly from an intact blastocyst. Finally, the researchers demonstrated the ability to efficiently initiate differentiation in suspension. These discoveries open the door to large-scale expansion of hESCs and subsequent directed differentiation for potential cellular therapies. Nature Biotechnology 28(4):361–4; laboratory of B. Reubinoff (privately funded in Israel). 2010 April.

***Zscan4* Regulates Telomere Elongation and Genomic Stability in Embryonic Stem Cells:**
Embryonic stem cells (ESC) have long telomeres, which are thought to play a vital role in ESCs' ability to self-renew without compromising their genetic integrity. NIH intramural scientists studied the gene *Zscan4*, known as a key marker for mouse ESCs' genetic stability and self-renewal. Until now, the theory of self-renewal was that ESCs divided into two completely unaltered daughter cells, including telomere length. However, the scientists observed that when the *Zscan4*gene is turned on in ESCs, it plays a role in "rejuvenating" the ES cell—lengthening the telomere, thus maintaining genetic stability. *Zscan4* is also actively expressed in induced pluripotent stem cells (iPSCs). If scientists can improve their understanding of how *Zscan4* works, these studies could have major implications for aging research, stem cell biology, and cancer biology. *Nature. 464(7290): 858–863, 2010*; laboratory of M.S.H. Ko at NIH's NIA (supported by the NIH Intramural Program). 2010 April 8.

How does an unspecified stem cell differentiate into a specific cell type? Scientists document which genes are transcribed during neural differentiation of hESCs:
In order for the instructions contained in our DNA (deoxyribonucleic acid) to be carried out, DNA must be transcribed into corresponding molecules ofribonucleic acid (RNA), referred to as transcripts. A transcriptome is a collection of all the transcripts present in a given cell. Messenger RNA (mRNA) transcribed from genes is delivered to ribosomes, which read, or "translate," the sequence of the chemical letters in mRNA to assemble building blocks called amino acids into proteins. Each mRNA is transcribed from a gene and then translated into a specific protein. DNA can also be transcribed into other types of RNA that do not code for proteins. Such transcripts may serve to influence cell structure and to regulate genes. NIH-supported scientists examined the RNA transcripts in cells at four points during *in vitro* differentiation: 1) the pluripotent state; 2) after neural initiation, when the cells are grown in conditions that drive them towards a neural fate; 3) the neural progenitor state, where cells can become either neurons or glial cells; and a final state, 4) where cells were fated to become only glial cells. Cells made fewer RNA transcripts as they progressed to more differentiated states. The scientists hypothesized that larger number of transcripts in hESCs may help them maintain pluripotency. The scientists used a technique called RNA-Seq, which was able to identify novel transcripts not detectable by other high-throughput screening methods. The novel transcripts were often highly correlated with the differentiation stage, and therefore may play a role in directing cell differentiation. Finally, the scientists also identified a number of genes with a developmentally-regulated time course, which



improve our understanding of neural differentiation. *PNAS 107(11): 5254–5259*; laboratories of M. Snyder, M. Gerstein, W. Cui and S. Weissman (NIH-supported). 2010 March 16.

Scientists influence stem-cell development with geometry:

Themicroenvironment plays a critical role in directing differentiation of stem cells. Scientists manipulated the microenvironment of mesenchymal stem cells (MSCs) to determine if this could influence cell fate. MSCs are multipotent and can differentiate into bone, cartilage, and fat. NIH supported scientists determined that they can influence differentiation of MSC cultures by forcing them to grow in a certain geometrical shape. Most MSCs grown in a star shape, which promotes a tensecytoskeleton, become bone cells. Most MSCs grown in a flower shape, which promotes a loose cytoskeleton, become fat cells. Scientists now plan to test whether this method works in stem cells derived from other sources. *PNAS107(11): 4872–4877*; laboratory of M. Mrksich (NIH-supported). 2010 March 16.

One Stem Cell Does Not Give Rise to all Components of the Blood:

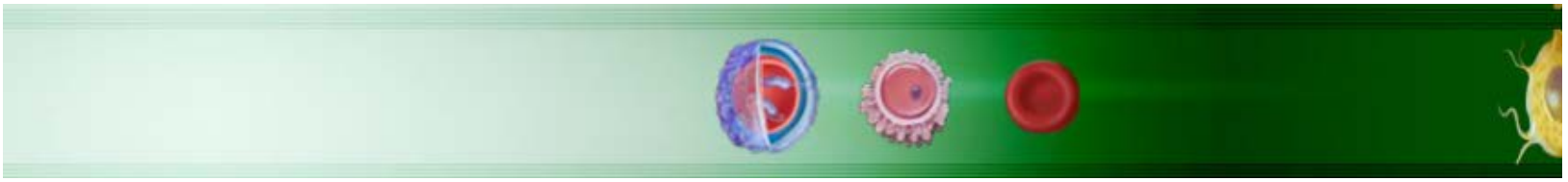
Textbooks describe a single type of stem cell that is capable of producing all the cells present in the bone marrow. A recent publication challenges this fact. NIH-funded scientists identified 3 subtypes of bone marrow stem cells, based upon their release of dye, their geographical location within the bone marrow stem cell population, and the types of cells they generated following transplantation of a single cell into mice. This discovery has significant implications for scientists hoping to better understand how blood-forming stem cells arise, and to improve therapies that use human blood-forming stem cells. *Cell Stem Cell 6: 265–278*; laboratory of M. Goodell (NIH-supported). 2010 March 5.

Differentiate or Self-Renew? Opposing Molecules Responsible for Controlling Fate of Mouse Embryonic Stem Cells:

microRNAs (miRNAs) are short non-coding RNAs (don't make proteins) that regulate genes. The ESCC miRNA family is important for maintaining a stem cell's ability to self-renew. ESCC miRNAs are highly expressed in embryonic cells, but are down-regulated in cells that are differentiating. The let-7 microRNA family seems to play in an important role in differentiation. Let-7 miRNAs are not expressed in embryonic cells, but are highly expressed as cells undergo differentiation. Thus, ESCC and let-7 miRNAs seem to have opposite functions. Building on this data, scientists tested members of the let-7 family to determine if they blocked the self-renewal action of the ESCC microRNAs in mouse embryonic stem cells. The let-7 family did block self-renewal, and adding in a representative member from the ESCC microRNA family reversed this effect. Thus, scientists have identified two opposing families of microRNAs that are vital to stem cell self-renewal and differentiation. *Nature 463: 621–626*; laboratory of R. Blelloch (NIH-supported). 2010 Feb 4.

Generation of Human Induced Pluripotent Stem Cells (iPSC) Reverses Defect in Individuals with Rare Genetic Disorder:

Induced pluripotent stem cells (iPSCs) are known to have longer telomeres, which is thought to play a role in their ability to self-renew. To better understand this process, NIH-funded scientists have created iPSCs from skin(fibroblast) cells from individuals with Dyskeratosis congenita (DKC). DKC is a rare progressive disease that typically causes bone marrow failure and is characterized by a genetic defect that affects telomere function. The scientists discovered that the DKC-derived iPSCs did not exhibit the DKC genetic defect and showed normal telomere function. However, once the iPSCs differentiated into specialized cells, the DKC genetic defect reappeared and telomere function was again faulty. The results of the study show that the ability for iPSCs to self-renew compensated for the DKC genetic defect, but the mature cells reverted to the diseased state. If scientists can understand how iPSC reprogramming affects the function of cells, treatments could be developed



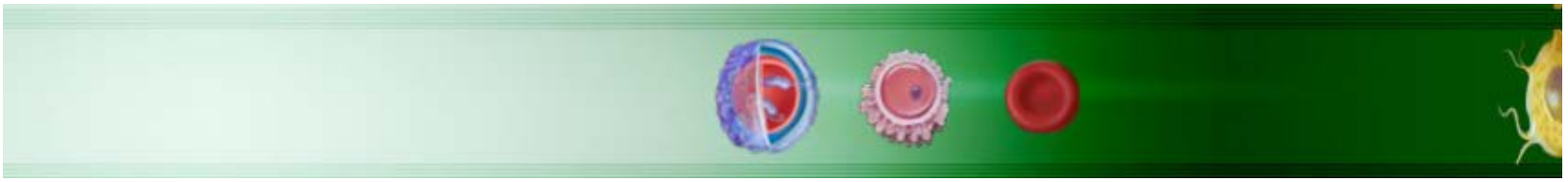
for individuals with DKC and similar diseases. *Nature* [Epub ahead of print]; laboratory of G.Q. Daley (NIH-supported). 2010 Feb 17.

hESCs vs. iPSCs: iPSCs Demonstrate Variable Potency and Efficiency in Making Neurons and Glia:
Since the first report of human induced pluripotent stem cells (iPSCs) in 2007, laboratories have been working to compare the abilities and usefulness of hESCs to iPSCs. Recently, some of the same scientists who first generated human iPSCs compared the ability of iPSCs vs. hESCs to differentiate into neural cells (neurons and glia). The scientists demonstrated that both hESCS and iPSCs follow the same steps and time course during differentiation. However, although hESCs differentiate into neural cells with a similar efficiency regardless of the cell line used, iPSC-derived neural cells show greater variability in differentiating into neural cells, and lower efficiency in the process, too. This was true regardless of which of several iPSC-generation protocols were used to reprogram the original cell to the pluripotent state. Experimental evidence suggests that individual iPSC lines may be "epigenetically unique" and predisposed to generate cells of a particular lineage. However, the authors believe that improvements to the culturing techniques may be able to overcome the variability and inefficiency they described in this report. *PNAS Early Edition*; laboratory of S.-C. Zhang (NIH-supported). 2010 Feb 16.

Nuclear Receptor Nr5a2 Can Replace One of the Four Original Factors Used in iPSC Reprogramming:
The original protocol for reprogramming adult cells into induced pluripotent stem cells, or iPSCs, included four factors: Oct4, Sox2, Klf4, and c-Myc. Since the initial iPSC publication, scientists have determined that each of the original factors can be replaced by other similar factors, except for Oct4. Now, scientists conducting a screen to identify factors to enhance reprogramming determined that the nuclear receptor, Nr5a2, can replace Oct4 in the generation of iPSCs. Use of Nr5a2 can also increase reprogramming efficiency when added to the 4 traditional reprogramming factors. *Cell Stem Cell 6: 167–174*; laboratory of H-H Ng (non-NIH-supported). 2010 Feb 5.

Developmental map of hESC Epigenome
All cells in the body carry the same genetic information; however, that information is not active in all tissues throughout development. Epigenetics is the process by which cells control which of their genes is turned on or off, thereby determining the cell's function. DNA methylation is one important indicator of the epigenetic state, and is strongly associated with the silencing of a gene. In this study, scientists compared DNA methylation across the entire genome in 3 types of cells: hESCs, hESCs that were differentiated into skin fibroblasts, and in newborn skin fibroblasts. They noted several new methylation phenomena in this study. In certain cases, DNA methylation enhanced, rather than silenced, nearby gene activity. They noted quick transitions along the length of the DNA from high to low methylation states at exon/intronboundaries, suggesting a possible role for methylation in RNA splicing. Finally, the scientists observed that known developmental and pluripotency genes were differentially methylated across differentiation states. This is the first comprehensive map of the epigenetic changes that occur during cellular differentiation. This publicly available information may help scientists to predictably guide pluripotent cells towards a specific cell fate, an important step in the potential field of regenerative medicine. *Genome Research* advance publication; laboratories of I. Rigoutsos, J. Loring, and C. Wei (NIH-supported). 2010 Feb 4.

Adult Mouse Fibroblasts Directly Reprogrammed to Become Functional Neurons:
In 2008, NIH-supported Harvard scientists used 3 genes to directly reprogram adult mouse exocrine cells from the pancreas into cells that function as insulin-secretingβ-cells *in vivo*—without first taking them to a pluripotent state. Now, NIH-supported scientists at Stanford University used 3 neuronal genes to reprogram



mouse embryonic or perinatal fibroblasts directly to functional nerve cells, or neurons, *in vitro*. Electrophysiological studies revealed that the converted cells possessed properties consistent with those of cortical neurons, including the formation of functional synapses that respond to the neurotransmitters glutamate and GABA. Thus, direct reprogramming seems to be an effective way to generate a desired cell type in more than one organ system. *Nature advance online publication* ; laboratory of M. Wernig. 2010 Jan 27.

Transplanted Human Stem Cells Improve Repair of Major Bone Injuries in Rats:

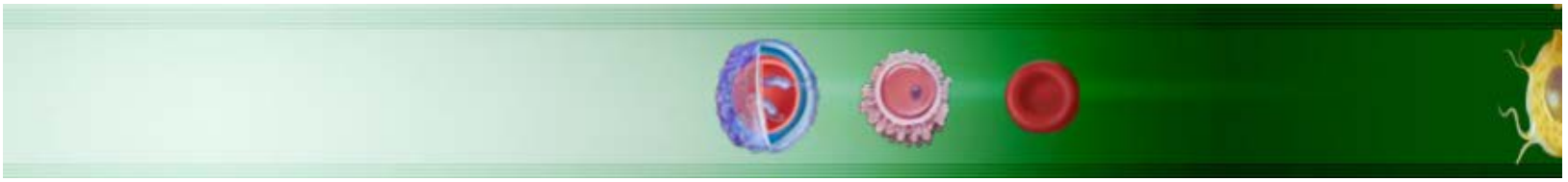
Bone grafting is a surgical procedure that places new bone or a replacement material into spaces around broken or defective bone to aid in healing. Previous studies have shown that both animal and human stem cells can be used as suitable substrate for replacing bone. In this study, NIH-supported scientists demonstrate the use of human non-embryonic stem cells (bone marrow-derived mesenchymal cells and amniotic fluid fetal stem cells) to repair bone in rats. The scientists implanted polymer scaffolds into a gap in the bone of both of the animal's legs, seeding some with stem cells and leaving other bone gaps with only the scaffold. After 12 weeks, scaffolds with stem cells produced more one and filled the gaps better than the scaffold alone. However, for both types of stem cells, the extent of bone gap repair was inconsistent. The scientists are now examining post-implantation survival or migration of the cells as possible explanations. If this treatment can be standardized, it may offer a potential alternative to bone grafting operations. *PNAS Early Edition*; laboratory of R.E. Guldberg. 2010 Jan 19.

Expanding Cord Blood Stem Cells:

Transplantation of hematopoietic stem cells from cord blood is a proven technique to treat certain leukemias. However, the cord blood stem cells often take more than 4 weeks to fully engraft, leaving individuals vulnerable to infection. Scientists hypothesize that the engraftment period could be reduced by expanding the total number of stem cells in cord blood units, but previous efforts to expand cord blood stem cells have been unsuccessful. In this study, scientists cultured the cord blood stem cells in the presence of a protein called Notch, which is involved in embryonic development. This method increased the total number of cord blood stem cells more than 150-fold, and the expanded stem cells were able to engraft intoimmunodeficient mice. The scientists then tested this technique in a phase 1 clinical trial. Following myeloablation, individuals were infused with one normal unit of cord blood and one unit expanded using the new culturing technique, rather than the current standard of care of two normal cord blood units. Individuals receiving the expanded unit demonstrated quicker engraftment, recovering the ability to make white blood cells in approximately 2 weeks. This research is the first to demonstrate a way to expand cord blood stem cells and is a significant step forward toward the clinical application of cord blood for the treatment of disease. *Nat Med 16(2):232–6*; laboratory of ID Bernstein. 2010 Jan 17.

Cancer Stem Cells Suppress Immune Response:

Glioblastoma multiforme is the most lethal type of brain cancer, being highly resistant to both chemotherapy and radiation. Individuals with glioblastoma also demonstrate immune system impairments. Scientists hypothesized that these impairments are caused by a small population of stem cells within the tumor. They now report that they have isolated a population of glioblastoma stem cells and determined that these cells suppressed the immune system response by affecting T cells in 3 ways: blocking their responses, inducing them to change their functions, and causing them to undergo apoptosis. These immunosuppressive effects could be reduced by inducing the cancer stem cells to differentiate into the three types of neural cells: neurons, astrocytes, and oligodendrocytes. Understanding how glioblastoma stem cells



evade the immune system will help scientists develop better treatments for glioblastoma multiforme. *Clin Cancer Res 16(2):461–73* ; laboratory of AB Heimberger. 2010 Jan 15.

Modeling Human Diseases in Human Embryonic Stem Cell Lines:

Although animal models of human diseases provide valuable scientific information, species differences sometimes mean that cures developed in animal models are not successful when tested in humans. Human embryonic stem (hESCs) cells offer a potential way to study human disease in human cells, but scientists have found it difficult to make disease-bearing hESC lines. The current method, using homologous recombination to replace the hESC's copy of a gene with a disease-bearing version, suffers from a low success rate, and does not always affect both copies (alleles) of the gene of interest. California Institute of Regenerative Medicine (CIRM)-funded scientists developed an improved method of homologous recombination that usesBacterial Artificial Chromosomes (BACs) modified to carry the desired human disease genes into the hESCs. Within the BAC, DNA sequences flanking the human disease-bearing gene improve its chances of undergoing homologous recombination, thus replacing one copy of the gene in the hESCs with the modified "disease-carrying" copy. Repeating the process a second time can replace the second allele of the gene of interest with the modified gene, so both alleles can be modified. Using the BAC method, the scientists achieved success 20% of the time, as opposed to 1% success in standard homologous recombination. The method worked in more than one hESC line, and cells produced from disease-bearing hESC lines have shown some characteristics of the intended human disease in initial tests. This new technique will enable scientists to rapidly develop human disease-carrying hESC lines. *Cell Stem Cell 6: 80–89*; laboratory of Y. Xu. 2010 Jan 8.