BEDFORD STEM CELL RESEARCH FOUNDATION

Massachusetts 501(c)(3) not for profit organization
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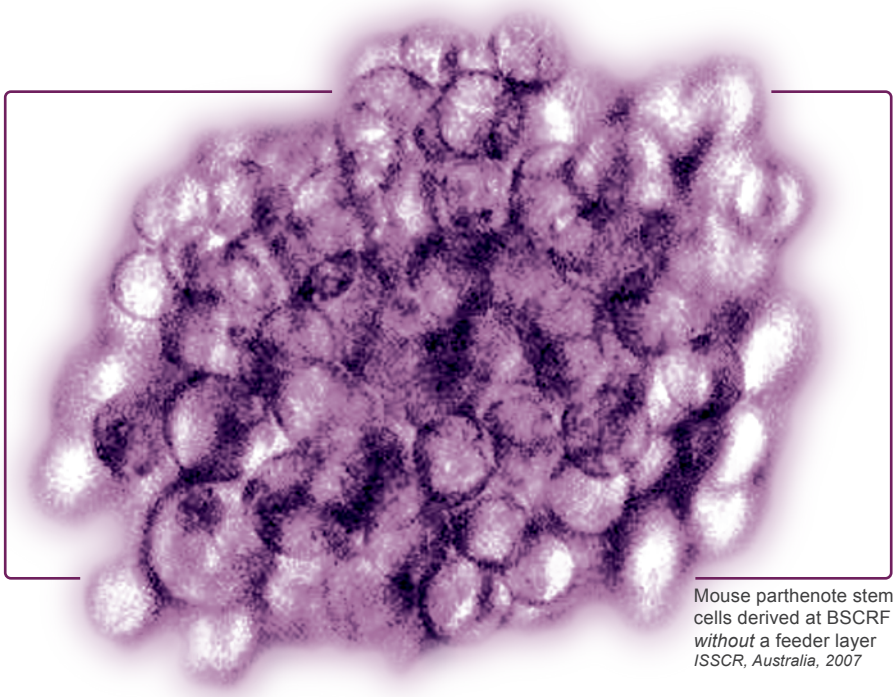
NEWSLETTER

Mouse Parthenotes

Derived without a feeder layer

Most human stem cell lines were developed on top of a "feeder layer" of mouse cells, thus rendering them *contaminated* with animal products. But these cells, derived by BSCRF scientists *without* a feeder layer bring us one step closer to overcoming this important obstacle to stem cell therapy.

Inside This Issue



Mouse parthenote stem cells derived at BSCRF *without* a feeder layer
ISSCR, Australia, 2007

The Potential for Miracles

Recent advances in stem cell research have raised the hope of curing diseases once believed to be incurable: heart failure, spinal cord injury, diabetes, Alzheimer's, Parkinson's, AIDS. These diseases are the result of the death of specific types of cells, such as nerves and the cells in the pancreas that produce insulin. For reasons that are not understood, new cells do not automatically replace defective cells in some tissues such as spinal cord, brain and pancreas.

Other tissues, such as skin and blood, routinely replace dying cells with new cells recruited from reserve supplies that maintain the potential to become active and multiply when needed. Such cells are called "stem cells."

Skin stem cells are examples of *adult* stem cells, so-called because they can become only *one* type of tissue, e.g. skin. In contrast, cells from early embryos are *pluripotent*, that is, they have the potential to become all types of tissues.

Experiments with laboratory mice have demonstrated that pluripotent stem cells can replace dead cells in all organs including the heart, which does not have its own supply of stem cells. These encouraging results have spawned studies to apply stem cell therapy to humans.

Founded in 1996, the Bedford Stem Cell Research Foundation is a biomedical institute that exists to conduct stem cell and related research for diseases and conditions that currently have no effective methods of treatment or cure.

Celebrating 10 Over 10 Years

BSCRF WINTER 2007 UPDATE

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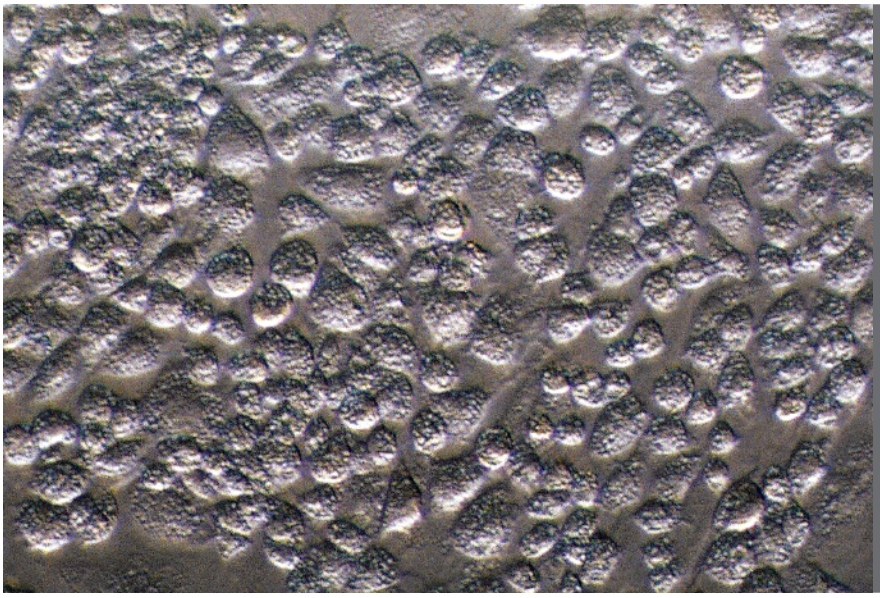


A New Source of Pluripotent Stem Cells?

Stem Cells From Adult Testis

Similar to embryonic stem cells, recent reports indicate that stem cells found in the adult mouse testis are *pluripotent*, meaning they have the potential to become *any* cell in the body.

Colony of stem cells derived from an adult mouse testis. Photo taken in the BSCRF lab on Nov. 7, 2007

Last year, a team of German scientists reported the isolation of pluripotent stem cells from adult mouse testis *(Nature: 440, April 2006)*. This report was followed by newspaper accounts of similar stem cells being isolated from adult *human* testis.

Bedford research scientists have years of experience in testis research and immediately followed up this report with new experiments. Initial promising studies at the Foundation used goat testis. Recently, Dr. Jeff Shaman replicated the experiments in mice by isolating stem cells from adult mouse testis (photo above). This important first step demonstrates that the testis may be a good source of *pluripotent* stem cells, thus providing another alternative to the use of ethically controversial embryonic stem cells. These adult stem cells, together with the Foundation's mouse parthenote stem cells, will allow for the investigation of differences between the testis and parthenote stem cells with the same genetic backgrounds. This will pave the way for the isolation of pluripotent stem cells from adult human testis.

New Talent at BSCRF

Dr. Jeffrey Shaman has joined the BSCRF scientific team to spearhead a new project deriving pluripotent stem cells from testis. This new, promising area of investigation complements the Foundation's ongoing work with parthenote stem cells from unfertilized eggs. Men produce millions of sperm every day for their entire lives, but until recently it was thought that those sperm arise from tissue-specific stem cells in the testis that could only give rise to sperm, not to pluripotent stem cells. More recent evidence, however, suggests that in addition to the stem cells that give rise only to sperm, there is another small population of stem cells that are *pluripotent* and can give rise to all body tissues. Like all stem cells in adult tissues, the pluripotent stem cells in the testis are programmed not to divide unless needed. The challenge to scientists is to understand how to not only *isolate* the pluripotent adult testis stem cells in the laboratory, but also how to coax them into a state of *continually dividing*, like stem cells derived from eggs.

Dr. Shaman is uniquely well suited to conduct these studies because of his excellent background studying the genetic and epigenetic information contained within sperm heads, as well as how the expression of sperm genes is controlled. He received a Master's degree from Rutgers and the University of Medicine and Dentistry of New Jersey, and his PhD from The Johns Hopkins School of Medicine in 2004. He then studied with Dr. Steven Ward at the University of Hawaii's Institute of Biogenesis Research, until joining the BSCRF team in 2007.

The foundation is also proud to welcome Jamie Thorn as part of our laboratory team. Mr. Thorn holds a BS in Biology from Suffolk University, with minors in Chemistry and Philosophy. He takes over for Bryan Desmarais as the cornerstone of the Foundation's award winning SPAR program. Mr. Thorn will participate in all clinical laboratory activities and head up the molecular biology assays utilized for HIV detection, Hepatitis B, C and bacteria.

BEDFORD STEM CELL RESEARCH FOUNDATION
CHANGING THE PACE OF PROGRESS

The Activated Egg SYMPOSIUM

November 9, 2007

On November 9, 2007, the annual symposium celebrated its sixth year, with keynote speaker Dr. Ian Wilmut.

Dr. Ian Wilmut's career began at the Animal Research Station in Cambridge, where he took his doctoral degree in animal reproduction, particularly cryopreservation of sperm and embryos. "Frostie" was the world's first calf born after freezing and thawing an embryo. As a young faculty member of the Roslin Institute, Dr. Wilmut focused on *"...the basic repertoire of reproduction - eggs, sperm, and embryos - with the aim of understanding the causes of early embryo death."*

Dr. Wilmut's latest book, *"After Dolly: The Uses and Misuses of Human Cloning"*

He became a genetic engineer in the early 80's with the goal of introducing new genes into domestic animals. Breeding domestic animals selects for thousands of genes at once, hence the difference between Dalmatians and Dachshunds. But the ability to introduce one gene at a time created an unparalleled research paradigm, far more powerful than a breeding program, because individual gene functions could be studied. Moreover, the products of individual genes could be *bioactive proteins* important to human health, such as blood clotting factors to treat hemophilia, and enzymes to eliminate blood clots during heart attack or stroke. The result of this work was "Tracy," a Scottish sheep who had been genetically engineered to express gram quantities of alpha-1 antitrypsin in her milk.

This proved the value of genetically manipulated livestock as sources of pharmaceuticals - "pharming." However, complex genetic manipulations of embryos was far more difficult than genetic engineering of cultured cells. To produce offspring from genetically modified cells, Ian had to first clone a non-modified cell. Along came Dolly.

"Cloning for me has always been a tool of science - finding out how cells work..."

Dr. Wilmut presented *"Cloning in the 10 Years Since Dolly"* at the 2007 Symposium. Other experts at the Symposium were Dr. Jose Cibelli, cow cloning pioneer; Dr. Steve Stice, an expert in embryonic stem cell differentiation; Dr. Barbara Knowles, an expert in mouse embryonic gene expression; Dieter Egli, Harvard University Research Fellow; Steven Sheridan, embryonic stem cell scientist with Millipore Corporation; Jeffrey Janus, President, and Nikolai Turovets, Senior Research Scientist of International Stem Cell Corporation, experts on human parthenote stem cells; and Dr. Robert Truog, chairman of Harvard University's Embryonic Stem Cell Research Oversight Committee.

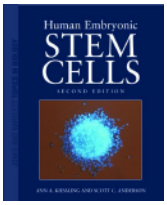
In 2002, the Foundation launched *The Activated Egg* symposium series. During this one-day event researchers studying eggs for reproduction, stem cell derivation, or animal cloning share and discuss their research. With attendance limited to 100 the event provides a unique environment for investigators from academia, industry and infertility clinics to meet and form collaborations.

A New Board Member

Sean Kealy, Esq. joined the Bedford Stem Cell Research Foundation Board of Trustees in September. Attorney Kealy was instrumental in drafting and promoting the Massachusetts stem cell bill in 2005 as a member of the State House staff of Senator Cynthia Creem who sponsored the bill. He co-edits an electronic newsletter, *Criminal Law Update*, and is on the faculty at Boston University School of Law.

Second Edition of HESC

Human Embryonic Stem Cells: An Introduction to the Science and Therapeutic Potential, 2nd Ed



Dr. Ann Kiessling and Scott Anderson's text remains the only introductory stem cell textbook, providing a single reference for basic information addressing the science of stem cells and the relevant social, legal and ethical debates.

How Much Does $1 Cost?

The Economics of Philanthropy

For every dollar we give to research, how much does it cost the tax payer?

Private funding of biomedical research not only sends a strong message to legislators, it directly funds more research. According to estimates from the *Office of Management and Budgets* website:

Source of one dollar	Cost to Taxpayer
Federal: *National Institutes of Health (NIH)*	***$1.50***
State: *Grants and Programs*	***$1.20***
Private Donation **Depending on income tax bracket.*	***$0.67****

Stem Cells 101

What Is A Stem Cell?

A reserve cell with the capacity to multiply when needed to replace dead or damaged adult cells. Reserve stem cells do not exist for many vital tissues, including: heart, spinal cord, brain and pancreas.

Key Term

"Pluripotent"
The capacity to become any cell in the body.

- Pluripotent stem cells show the most promise for use in stem cell therapies.
- Embryonic stem cells are pluripotent, adult stem cells are not.

Types of Pluripotent Stem Cells

It is still unknown which are best for therapies.

1) Embryonic stem cells from *fertilized* eggs are good models for research, but they have ethical issues, and will have tissue rejection problems (similar to bone marrow and kidney transplants).

2) Parthenote stem cells (derived from *unfertilized* eggs) may be as pluripotent as embryonic stem cells, and have been the focus of BSCRF scientists for several years. Studies using monkey parthenote stem cells to treat Parkinson's disease have been very promising.

- Parthenotes do not have the potential tissue rejection problems faced by stem cells derived from *fertilized* eggs.
- Unlike adult stem cells, parthenotes can potentially become any cell in the body.
- Less controversial than stem cells that are derived from *fertilized* eggs.

Changing the Pace of Progress...

BSCRF is the only independent, not for profit and non-federally funded Massachusetts resource for the advancement of stem cell and related studies.

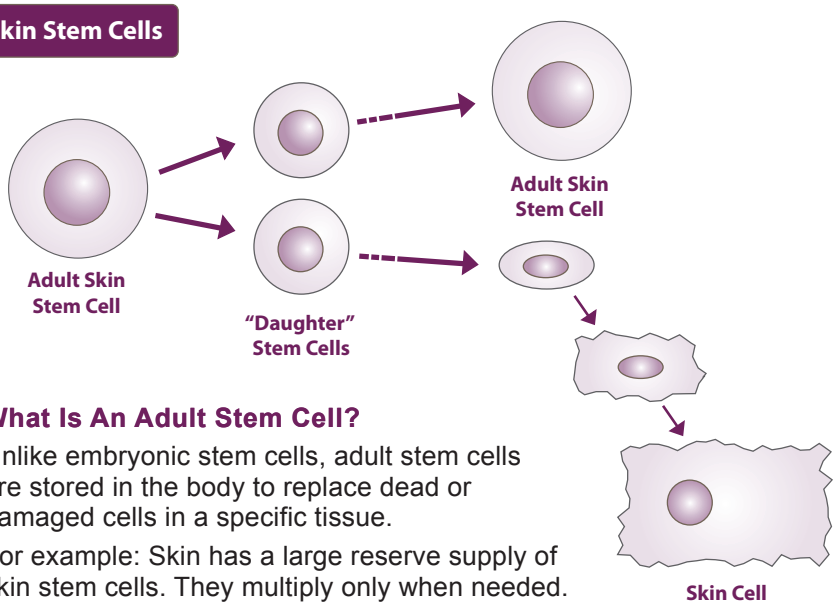
What Is An Embryonic Stem Cell?

A stem cell derived from eggs *fertilized by sperm;* these stem cells are "pluripotent." Recent research has shown that it may also be possible to get pluripotent stem cells from *unfertilized* eggs.

What Are Cord Blood Stem Cells?

Cells in the umbilical cord are "multipotent" and can give rise to all the cells in a normal bone marrow. Scientists are working to discover if these cells can become other types of adult stem cells.

Skin Stem Cells



What Is An Adult Stem Cell?

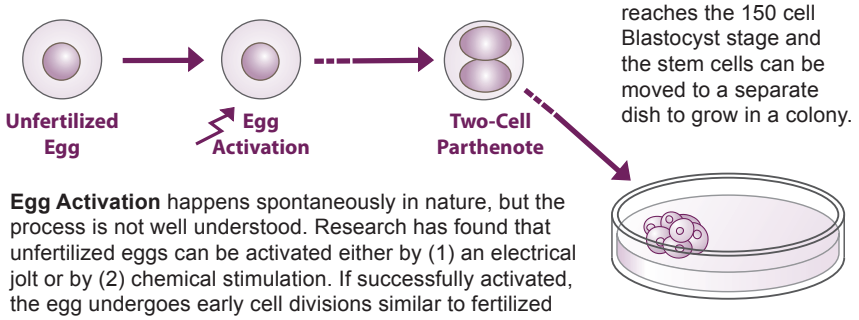
Unlike embryonic stem cells, adult stem cells are stored in the body to replace dead or damaged cells in a specific tissue.

For example: Skin has a large reserve supply of skin stem cells. They multiply only when needed.

Stem Cells From *Unfertilized* Eggs?

When eggs are fertilized by sperm they become "activated," their cells divide and can be a source of embryonic stem cells. However, BSCRF scientists have shown that human eggs can be "activated" without being fertilized. *Unfertilized*, "activated" eggs are called **Parthenotes**.

Parthenote Stem Cells



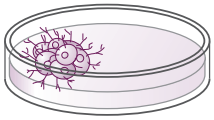
After approximately 6 days the parthenote reaches the 150 cell Blastocyst stage and the stem cells can be moved to a separate dish to grow in a colony.

Egg Activation happens spontaneously in nature, but the process is not well understood. Research has found that unfertilized eggs can be activated either by (1) an electrical jolt or by (2) chemical stimulation. If successfully activated, the egg undergoes early cell divisions similar to fertilized eggs, but cannot give rise to an offspring.

Results at BSCRF are promising. We have developed laboratory conditions that lead to mouse *parthenote* stem cells (mPS) with the same efficiency as from *fertilized* mouse eggs. Our most recent mPS cells were developed entirely in laboratory conditions free of other animal cells (cover photo), thus paving the way for similar development of human PS cells free of animal cells.

What Comes Next?

Parthenotes to Neurospheres



How do we turn on the genes that lead to nerve cells?

Neurospheres are an early stage of development of neurons from stem cells. At this early stage, they can be coaxed to differentiate into a variety of types of nerve cells (i.e. brain, optic, spinal, etc.).

To form neurospheres from mPS cells (mouse parthenotes), it is necessary to coax the mPS cells into silencing the genes that make them behave like stem cells, and turning-on the genes that lead to nerve cells. This is a multi-step process that can take months to accomplish.

To improve the speed and efficiency of this process, Bedford Foundation scientists are taking advantage of very recent advances in analyzing the expression of specific genes in cells. The method is termed "Micro-array Analysis," and allows the measurement of changes in the expression of 40,000 genes.

Promising Results

Bedford scientists have discovered that by using a drug already approved for human use, we can coax the mPS cells into expressing neuronal genes within two weeks. This exciting result needs to be repeated multiple times, but initial findings are highly promising.

ASRM 2007 Prize Paper

BSCRF's SPAR program receives the *Society for Assisted Reproductive Technology Prize Paper Award*, presented at the ***American Society for Reproductive Medicine*** annual meeting in Washington DC, 2007

Visiting the State House

The Ethics of Human Eggs

Since Dr. Kiessling's letter, "Eggs Alone" to to *Nature* in 2003, and her 2006 report in *Science* magazine "Ethical Oocytes: Available for a Price," it has become apparent that the dialogue between scientists, legislators and the public about the controversy surrounding Stem Cells and Human Eggs is becoming increasingly important.

June, 2007, the Foundation lead a legislative briefing at the Massachusetts State House entitled, "Stem Cells: Myths, Facts and Becoming a National Leader." During the standing room only presentation, Dr. Kiessling outlined a brief history of stem cell science, the controversy of human egg research, and an overview of state legislation that will enable this important research to move forward.

Controversial Work

The Ethics Advisory Board

Bedford Stem Cell Research Foundation is at the forefront of stem cell and related research. Founded in 1996, the Foundation has an established community of scientists investigating the potential for stem cell therapy.

BSCRF scientists rely on the Ethics Advisory Board to assist in understanding the complex ethical questions raised by some aspects of stem cell research. This board, like the Foundation's Board of Trustees, has no financial stake in the research; the progress of the science and the health of those afflicted are their primary concern.

Discovering a New Angle

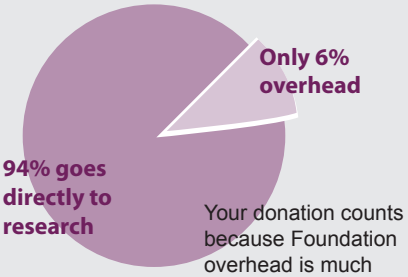
Unlike most of the "embryonic" stem cell research conducted in the United States with "left-over" embryos in fertility clinics, BSCRF's research efforts focus on using *unfertilized* human eggs to derive *pluripotent*, *parthenote* stem cells.

In parallel with the parthenote work, BSCRF scientists have launched an effort to derive stem cells from *adult testis*, following up a report in 2006 that the testis contains not only stem cells that give rise to sperm, but also a small population of *pluripotent* stem cells.

The Power Of Private Funding: Changing The Pace of Progress

The Bedford Stem Cell Research Foundation is a not for profit, 501(c)(3) organization.

The Bedford Research Foundation has lower operating costs than large teaching and medical institutions. For this reason, more research results from each donation received.



Your donation counts because Foundation overhead is much lower than many institutions. 94% of donations go directly to research.

Living Endowment

The Bedford laboratory is not only a research lab, but also a clinical laboratory. The lab provides a variety of highly specialized testing services, many of these test are unique in the world. Revenues from these tests help support ongoing research efforts.

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Getting Involved

BSCRF research cannot be funded by federal grants-in-aid because of the U.S. funding moratorium. BSCRF has lower operating costs than larger teaching and medical institutions. For this reason, funds are utilized more efficiently, and more research results from each donation.

Your contribution could help everyone you know.

The tax-exempt status granted to qualified public charities highlights the U.S. Government's belief that taxpayers have the right to directly support activities they feel are important. To advance the treatment opportunities, to maintain and grow its community of scholars and scientists, to enlarge the potential for miracles, the Foundation needs private benefactors to raise funds to continue its mission.

Challenge Grant: Help us meet our $280,000 matching fund! The $560,000 a year will fund a team of scientists to develop improved methods of generating neurospheres from pluripotent stem cells.

Please mail contributions to:

Bedford Stem Cell Research Foundation

PO Box 1028
Bedford, MA 01730

Please enclose the name and address of anyone you would like to be notified of your contribution or added to our mailing list.

Donate Online at:
www.bedfordresearch.org

Your Support is Greatly Appreciated!

Please don't hesitate to contact us with any questions.

ABOUT THE DIRECTOR

Dr. Ann Kiessling has pursued her dual interest in virology and reproductive biology since receiving her doctorate from Oregon State University. She has published over one hundred scientific papers covering both areas of research and is Associate Professor of Surgery at Harvard Medical School.

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STEM CELL RESEARCH UPDATE

- **The Parthenote Project:** Over 40,000 genes could contribute to the development of parthenotes for stem cell therapy - the question is: Which ones?
  Find out how the Foundation's latest research initiative is narrowing down the list.

- **Stem Cells From Adult Testis?** Foundation researchers have initiated studies to verify new reports of stem cells from adult testis. *These cells hold the promise of alternate sources of stem cells.*