STEM CELLS Research

Costs / Benefits / Ethical Debate

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THERAPEUTIC POTENTIAL AND MORAL CONTROVERSY

The Key to Regenerative Medicine?¹

The medical community has long sought methods to replace cells irreparably damaged by disease or injury. In recent years, stem cell research has become an integral part of this quest. Stem cells differ from the rest of the body’s cells in two ways. First, they have the ability to proliferate (i.e. renew themselves over extended periods of time). Second, they are unspecialized, and have demonstrated that under some controlled conditions, they can be transformed into cells performing specialized functions via a process called differentiation. Therefore, stem cells could be the theoretical replacements for damaged specialized cells, which are otherwise unable to renew themselves.

Scientists have documented two types of stem cells – adult and embryonic. Until recently, scientists believed that adult stem cells could only evolve into the cell type of the tissue in which they were found. This position has been qualified in the last few years, however, when several experiments revealed the “phenomenon known as plasticity,” in which adult stem cells from one tissue appeared to be able to transform themselves into cells of totally different tissue types. While this previously undiscovered potential has generated a significant level of excitement within the research community, the actual therapeutic value of adult stem cells remains the subject of scientific debate.
Embryonic stem cells – logically found within embryos – have demonstrated their ability to proliferate within a laboratory and remain undifferentiated, which adult stem cells have not been able to do. For this reason, embryonic stem cells have been considered the more promising of the two stem cell types; however, extraction of these stem cells necessitates the destruction of the embryo. While these cells have been taken exclusively from embryos formed in vitro, not from eggs fertilized in utero, and have been provided by consenting donors, they have become the main focus of the groups opposed to stem cell research.

**The Ethical Debate**

The most vocal opponents of embryonic stem cell research are overwhelmingly against abortion, and in fact employ the same argument as the pro-life movement does: human life begins with conception, and therefore embryos are (or are at least equivalent to) human beings. Any research requiring the destruction of an embryo, they argue, is morally wrong.

Conversely, advocates of embryonic stem cell research refer to the frequent failure of fertilized eggs to “implant in the uterus.” They claim that although embryos may indeed have the potential for human life, they certainly should not be considered human beings unless they have attached to the uterine wall. Therefore, embryos created outside of the female body – via in vitro fertilization – are acceptable sources of stem cells.

Regardless of any potential absolute morality, the advocates of embryonic stem cell research may have logic on their side. Currently, in vitro fertilization clinics produce far more embryos than are actually used in their fertility treatments. These remaining embryos can be stored at a cost to the genetic parents, but in many other cases, they are discarded by the clinic. Research proponents argue that it must be “morally permissible to use such embryos
for potentially life-saving biomedical research”; serving as such invaluable research material must be of a higher moral value than suffering otherwise useless disposal.

The opponents eschew this logic in favour of a position that places moral consistency above utilitarian practicality. They acknowledge that the disposal of these embryos is certainly useless, and could instead be quite valuable to well-intentioned research. However, the opponents maintain that even research based only on embryos that will be destroyed anyway would effectively condone the destruction itself.

Since recent experiments on adult stem cells have revealed therapeutic potential previously thought to be exclusive to embryonic stem cells, opponents argue that embryonic research is now fundamentally unnecessary. To some degree, this mentality has been adopted by some of the advocates of unrestricted stem cell research as well. A subpopulation of the pro stem cell research movement has concluded that the focus on embryonic stem cells may have been somewhat misguided. In 2003, Proneuron Biotechnologies began conducting clinical studies on an experimental therapy for spinal cord injuries. Doctors used macrophages – scavenger cells found within the bloodstream – to promote spinal cord regeneration in patients whose injuries had been sustained within two weeks of the treatment. The treatment was a moderate success in several of its subjects, and it did not require the use of embryonic stem cells.

Other Risks of Stem Cell Research

In addition to the abovementioned ethical concerns, there are critics who claim that stem cell research should not be pursued based on scientific reasoning. They assert that the replication of stem cell development may cause unknown detrimental side affects that outweigh any possible (and as yet unclear) benefits. At the forefront of this argument is the concern that
therapeutic cloning may actually result in the creation of cancer producing cells. If this were the case, stem cell research for the ultimate use in humans for treatment of diseases would never be beneficial. A second argument is that even if the cells were not cancer producing, the quality of the cloned cells may never be as good as the original. Proponents of stem cell research hope to determine the answers to these questions through stem cell research.

WILL STEM CELLS HEAL?

*Diabetes*

Diabetes remains a worldwide health concern for which no known cure has been discovered. Diabetes is a disease in which the body is unable to manage blood glucose levels, specifically letting them rise to abnormally high levels, which then has detrimental long-term effects.

Most diabetes research is focused on treatment and management of the disease through insulin delivery and monitoring. Transplantation, either of the pancreas or of the insulin-producing islet cells (successful human islet transplantation was reported in July 2000⁴), is the closest cure that a diabetic currently has available. However, neither pancreases nor islet cells are readily “available” to the diabetic population nor is a patient guaranteed that his/her body will not reject it (though this does not seem to be the case with islet transplantation).

Because of the limitations of transplantation and the lack of other options, there has been a strong push from doctors, scientists, organizations such as the Juvenile Diabetes Research Foundation, diabetics and their families to find a cure through stem cell research. Supporters believe that stem cells are the key to creating insulin-producing cells which would not be rejected by the host when transplanted. They hope to discover a way to make pancreatic tissue or insulin-producing cells multiply, effectively creating an unlimited cure of diabetes. Some recent studies have shown that this may not be just a pipe dream. Perhaps the most
promising came from a team at Toronto University: they were able to identify multipotent precursor cells (immature cells that have the potential to differentiate into many different types of cells) from the adult mouse pancreas which proliferated in vitro to form and differentiate into beta-like cells producing insulin. Findings such as these further encourage proponents of stem cell research in the search for a cure of diabetes.

It should also be noted that while many supporters are strong advocates of embryonic stem cell research, some progress has been made in the development of adult cells into insulin-producing cells. A group from the University of Florida has found that bone marrow (“BM”) cells have the capacity to differentiate into a variety of cell types including endocrine cells of the pancreas. Their findings show that the adult BM cells are capable of transdifferentiating into a pancreatic lineage in vitro and may represent a pool of cells for the treatment of diabetes mellitus. Adult stem cells seem to provide another avenue for those seeking a cure for diabetes.

Finally, there also exists controversial research which claims that neither embryonic nor adult stem cells will be the answer for the cure of diabetes. A group at Harvard University claims that pre-existing beta-cells are the major source of new beta-cells (which produce insulin) during adult life and after pancreatectomy in mice. These results suggest that terminally differentiated beta-cells retain a significant proliferative capacity in vivo and cast doubt on the idea that adult stem cells have a significant role in beta-cell replenishment.

The vast expanse of research currently being conducted in the area of diabetes clearly shows not only the strong demand for a cure, but also the feeling in the industry that the cure is more closely attainably than previously imagined. Certainly, many avenues are being explored and stem cell research, both embryonic and adult, seem very promising.
Spinal Cord Injuries

A healthy spinal cord serves as the connection between the body and the brain; the latter controls the former by issuing millions of targeted electrical signals. Unlike the other organs of the human body, the spinal cord cannot repair itself, and serious damage to it often results in paralysis, a devastating condition in which thousands of Americans currently find themselves. While damage to the spinal cord is currently irreversible, stem cells appear to offer a new hope to the afflicted.

The spinal cord is part of the central nervous system. Most of the cells in this system (neurons) are created during the embryonic and early postnatal stages of human development; however, scientists have recently determined that neurons are steadily generated in two regions of the adult brain. While these naturally generated stem cells do react to injured spinal cords, they do not currently proliferate to repair the broken neural connection. Scientists reasoned that by somehow modifying this natural process, they could create astounding new treatments for paralysis.

Early applications of stem cell research appear to offer some hope to people with damaged spinal cords. In Korea, a team of researchers recently claimed that a 37-year-old spinal cord injury patient was able to walk for the first time in nearly twenty years with the help of their stem cell therapy. In this case, researchers used stem cells extracted from an umbilical cord. In addition to effectively sidestepping the controversy surrounding embryonic stem cells, the researchers claim that cord stem cells are slightly less omnipotent, and therefore less likely to proliferate into cancer cells.
Parkinson’s Disease

Parkinson’s disease is a neurological condition which affects the motor system. It is believed to be caused by the degeneration of a group of nerve cells in the brain which causes dopamine loss. Today, there is no way to stop or cure this degeneration; there are only treatments to help the symptoms.

Proponents of stem cell research for Parkinson’s believe that stem cells provide the means to replace the damaged cells. Perhaps one of the more promising findings came from a study conducted (summer 2004) by a team from Israel’s Hadassah University. They claim to have developed, for the first time, human embryonic stem cells into the nerve cells that are damaged or destroyed by Parkinson’s. Their experiment showed a reduction of Parkinson’s symptoms (an improvement of behaviour) in rats after transplantation of the human stem cells which became dopamine-producing cells.¹¹

This particular study also claimed that the cells did not continue to proliferate, nor did tumors develop. Experiments such as these, which produce positive results with no apparent side effects, provide the impetus for proponents of stem cell research.

WHERE DOES THE WORLD STAND?

Stem Cell Research in the United Kingdom¹²

Stem cell research first appeared in the laws and policies of the United Kingdom in the 1990s. Parliament passed the Human Fertilisation and Embryology Act in April 1990, also known as the 1990 Act, which allowed embryo research. The laws passed allowed for embryos up to 14 days old to be used for five categories of research, all relating to fertility.¹³
The Human Fertilisation and Embryology Authority (“HFEA”) was created in August 1991 as a result of the 1990 Act. According to its website, “the HFEA is a non-departmental government body that regulates and inspects all UK clinics providing IVF, donor insemination or the storage of eggs, sperm or embryos. The HFEA also licenses and monitors all human embryo research being conducted in the UK.” The HFEA is responsible for controlling the creation and use of embryos in research. In the UK, it is illegal to produce embryonic stem cells without first obtaining the right (and license) from the HFEA.

In December 2000, the British government passed a law permitting the cloning of early embryos to provide stem cells for experimentation and medical treatments. In February 2002, with the approval of a House of Lords committee, that the UK Parliament voted to allow therapeutic cloning and end a ban on stem cell research using human embryos. In doing so, the UK became the first country in the world to allow research on human embryonic stem cells and to allow limited cloning (up to fourteen days) of human embryos. However, the country did, and still does, have a ban on reproductive human cloning (i.e. cloning which would result in the development of a fully formed human).

Only one month after the enactment of therapeutic cloning, HFEA granted the first two embryonic stem cell research licenses to the University of Edinburgh's Center for Genome Research and to Guy's Hospital in London. The Edinburgh researchers plan to investigate treatments for conditions such as Parkinson's disease, while Guy's Hospital scientists will seek to develop treatments for infertility and miscarriage. Both will attempt to create stem cell lines from embryos discarded after in-vitro fertilization treatment. As of 2002, neither planned to perform therapeutic cloning and any stem cell lines created would be deposited into the national stem cell bank.
When the national UK Stem Cell Bank was established in September 2002, the UK was further cemented as the leading proponent of stem cell research (since this was the first bank in the world of its kind). This bank was established in Hertfordshire at the National Institute for Biological Standards and Control to serve as a repository for frozen adult stem cells, fetal stem cells and embryonic stem cells, including:

- Stem cells derived from leftover embryos created through in vitro fertilization
- Embryos created specifically for their stem cells; and
- Embryos created through cloning.

The Medical Research Council (MRC) provides the primary funding of the bank (75%) while the Biotechnology & Biological Sciences Research Council (BBSRC) provides additional support (25%).

In addition to the role it plays in the governing/running the UK Stem Cell Bank, the MRC also funds three year strategic grants for the establishment of high quality resources for stem cell research, funds approximately 12 training awards per year, and coordinates an International Stem Cell Forum each year. In 2002, MRC was awarded 40 million pounds of funding for stem cell research from the UK government across all of these areas.

In June 2003, HFEA granted the first license for human embryonic research to Roslin Institute to improve the technology to produce and maintain human embryonic stem cells in culture. These stem cells created were planned for research purposes only, including the possible testing of the safety and effectiveness of new medicines and the study of congenital disease. As with earlier licenses, sample of any stem cell line derived would be deposited in the UK Stem Cell Bank.
In August 2003, the first human embryonic stem cell line was created in the UK. As of September 2003, the national stem cell bank was reviewing the first applications to deposit the research-grade stem cells. At that time, the facilities for lines for therapeutetic purposes were not yet developed. In May 2004, the first stem cell lines (for therapeutic purposes) were deposited into the UK Stem Cell Bank.

In August 2004, HFEA granted its first license to clone human embryos in the UK for medical research using cell nuclear transfer, or therapeutic cloning. The scientists from the University of Newcastle will use eggs leftover from IVF treatment to clone these human embryos. While this law is considered to be the first of its kind issued in Europe, it is not the first in the world. Scientists from South Korea had announced earlier in the year that they had created 30 embryonic copies.

Today, the UK continues to be at the forefront of stem cell research. They are the most liberal proponent of stem cell research in the world. Though other countries are making strides in a similar direction, the UK currently maintains the greatest amount of activity in the field. *See Appendix 1 for a condensed summary of current licenses granted by HFEA*

**STEM CELL RESEARCH IN THE UNITED STATES**

*Federal Policy and Funding*

As the head of the Executive Branch of the U.S. Federal Government, which includes the National Institutes of Health, the President of the United States has the final responsibility and authority to set Federal government policy for funding human embryonic stem cell
research. However, Congress has appropriations authority and can possibly override the President's decision.

On August 9th, 2001, President George W. Bush announced that federal funds may be awarded for research using human embryonic stem cells if the following criteria are met:

- The derivation process (which begins with the destruction of the embryo) was initiated prior to 9:00 P.M. EDT on August 9, 2001.
- The stem cells must have been derived from an embryo that was created for reproductive purposes and was no longer needed.
- Informed consent must have been obtained for the donation of the embryo and that donation must not have involved financial inducements.xiv

In 2003, $25 million in federal funding was dispersed toward stem cell research.

**State Policy and Funding**

Although President Bush has limited federal funding, he is unable to direct the policies of individual states. Thus far, California and New Jersey have passed laws permitting funding of stem cell research. Additional states that are preparing similar legislation include Maryland, Massachusetts, Minnesota, New York, Pennsylvania, Rhode Island, Tennessee, and Washington. Other states, however, such as Arkansas, Iowa, Michigan, Nebraska, and North Dakota, have taken the opposite stance and have placed bans on several or all forms of embryonic stem cell research within their jurisdictions.xv

On November 2, 2004, Californians passed Proposition 71, a controversial bond measure that devotes $3 billion to human embryonic stem-cell experiments and comprises the biggest-ever state-supported scientific research program in the country. The passage of the measure will
likely put California at the forefront of the field and dwarfs all current stem-cell projects in the United States, whether privately or publicly financed.

While President Bush opposes most forms of stem-cell research, Republican Gov. Arnold Schwarzenegger backed Proposition 71, which funds embryonic stem-cell research at a state level. Scientists contend that Bush’s limited policy permits them only to work with embryos of poor quality. Thus, not only does the measure increase funding substantially, but also expands the scope of research to more-promising embryos. Proposition 71 authorizes the state to sell $3 billion in bonds and then dispense nearly $300 million a year for 10 years to researchers for human embryonic stem-cell experiments, including cloning projects intended solely for research purposes. It bans the funding of cloning to create babies.

The new funding is expected to create a maelstrom of activity in the field, affecting business and academia profoundly in the nation’s most-populous state. Stem cell start-up businesses are expected to emerge. At least one out-of-state biotech company is already making plans to move to California. Universities are hoping to recruit some of the field's brightest minds to take part in the biggest state-run research project in U.S. history. At the University of California, officials said the measure would help them attract top stem cell researchers to the state and encourage talented undergraduates to enter the field. Proponents and critics alike expect the new agency created under the ballot measure, the California Institute for Regenerative Medicine, to serve as a state version of the National Institutes of Health. But a myriad of questions remain to be resolved, as excitement from the election victory of Prop 71 now must be translated into action.

"California will be the epicenter of stem cell research in the future," said Dr. Edward Holmes, medical school dean at UC-San Diego. "Many people were reticent to move into this field, but this will attract some of the best and brightest young minds." Worcester, Mass.-based
Advanced Cell Technology, said it soon would open a California laboratory so it can apply for grants. Its chief executive has already moved to the San Francisco Bay area, and the company is trying to line up financing from California investors.

**Economic Impact**

While the costs of stem cell research are clear, the benefits are debated vigorously. Onlookers will be anxious to discover whether California’s funding will deliver the benefits promised by supporters of Proposition 71. Some question why venture capitalists are not willing to invest in stem cell research. "You're asking taxpayers to foot the bill for something that well-heeled venture capitalists are unwilling to put their own funds into," said Tim Rosales, a spokesman for Doctors, Patients and Taxpayers for Fiscal Responsibility. "If this holds such great promise, why aren't they investing?"

The answer is that they are not investing because benefits from stem cell research differ markedly for venture capitalists and governments. Governments will realize several benefits that VCs would not, making it much more feasible for funding to be provided by states. For example, venture capitalists would not benefit from the additional jobs and tax revenue generated by the funding. Furthermore, improving public health, potentially saving millions of lives and decreasing health care costs, is not a fully measurable benefit and certainly not one that venture capitalists can include in their ROI calculations. Additionally, California’s funding will attract many of the brightest minds and best companies in the field as a result of the funding. Biotechnology companies will cluster in California just as technology companies largely have situated themselves in Silicon Valley. California is already seen as a leading center for technological innovation, attracting talented venture capitalists, young engineers, and companies in related or supporting industries from all over the globe. This technology cluster is difficult to replicate and is self
reinforcing. With the passage of Prop 71, California will enjoy a first-mover advantage in all fields related to stem cell research, which could yield enormous positive externalities.

Proposition 71 provides total state revenues and health care cost savings of between $6.4 billion and $12.6 billion during the payback period, generating a 120% to 236% return on the investment made in the research on a total payback cost of about $5.4 billion, according to a study prepared for the campaign. Specific revenues and savings that are modeled include:

- **Direct income and sales tax revenues of at least $240 million** from the Initiative’s spending on research and research facilities.

- **Additional income and sales tax revenues of from $2.2 billion to $4.4 billion** if Proposition 71 could bring about even a 2.5% to 5% increase in private investments and research activity in the California biotechnology industry by making California a world leader in stem cell research.

- **Direct health care cost savings to the State government of at least $3.4 billion to $6.9 billion**, based on modest assumptions that the research would reduce state spending by at least 1% to 2% for the care and treatment of patients suffering from six medical conditions that scientists believe could benefit from the development of new stem cell therapies, including stroke, heart attack (acute myocardial infarction), insulin dependent diabetes, Parkinson’s disease, spinal cord injury, and Alzheimer’s disease.

- **Additional billions in health care cost savings for California businesses, citizens and other payers of health care costs.** California’s total health care spending costs now exceed $110 billion per year, including direct state government costs, costs funded by federal programs, insurance companies, employers, and individual citizens. In addition to providing billions in savings to the State government, new stem cell
therapies could reduce costs to other health care cost payers by $9.2 to $18.4 billion based on 1% to 2% cost savings for the six conditions considered.

- **State royalty revenues of from $537 million to $1.1 billion**, resulting from the provisions in Proposition 71 that give the state an opportunity to share in royalties resulting from research funded by the Initiative.

**Job Creation in California**

Direct spending from the Initiative will generate thousands of additional jobs in California. Additional growth in the biotechnology industry could generate additional jobs. In total, between 5,000 and 22,000 new jobs on average per year could be created; the total number of job-years (one job for one year = one job-year) ranges from 360,000 to 673,000.

**Enormous Upside Potential**

Given the promise of stem cell research, cost reductions of 10% or more in the six conditions considered are possible through significant improvements in therapies. Savings of 10% on health care costs would lead to additional saving to Californians of $92 billion and increase the total economic benefits to the State of Proposition 71 to 750% of cost.xvii

**CONCLUSION**

Stem cell research will continue to be conducted in the United States with or without federal funding. Furthermore, it will continue to be pursued around the world – in the hopes of curing diseases, reducing health care costs, or creating new drugs - until something devastating is encountered. Whether the pursuit is fiscally responsible or morally acceptable remains the subject of intense debate. The opponents and advocates are comparably fierce,
unquestionably dedicated, and likely to agree on one thing – the future of stem cell research is a matter of colossal importance.
## Appendix I*

<table>
<thead>
<tr>
<th>Institution</th>
<th>Project Description</th>
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<tbody>
<tr>
<td>St Mary's Hospital, Manchester Fertility Services and The University of Manchester - R0026</td>
<td>To investigate the way normal human embryos develop in the laboratory</td>
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<tr>
<td>University Of York R0067</td>
<td>To examine the development of the early human embryo</td>
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<tr>
<td>Clarendon Wing - Leeds RO104</td>
<td>To study the maturation of eggs in the laboratory setting</td>
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<tr>
<td>U C H London RO113</td>
<td>To discover more about this widespread chromosomal abnormality and how it may affect the development of the embryo; To devise tests to decide which eggs are the healthiest and most likely to lead to a normal baby</td>
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<tr>
<td>Section of Reproductive and Developmental Medicine R0115</td>
<td>To investigate the processes by which the early embryo forms the trophoblast - the cells which create the placenta and direct the embryo to implant in the uterus</td>
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<tr>
<td>Institute for Stem Cell Research R0132</td>
<td>To establish so-called trophoblast stem cells and embryonic stem cells from human embryos</td>
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<tr>
<td>London Fertility Centre</td>
<td>To study the molecular mechanism of immortality of embryonic stem cell lines; To understand the molecular pathways that drive stem cells into different cellular types</td>
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<tr>
<td>Oxford Fertility Unit RO143</td>
<td>To understand how to maintain stem cells in culture, and how to promote them to develop into different cell types</td>
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<tr>
<td>Princess Anne Hospital R0144</td>
<td>To generate human ES cells based on knowledge of culturing comparable cells, human embryonic germ (EG) cells</td>
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<tr>
<td>Newcastle Fertility Centre at Life R0145</td>
<td>To study embryos at different stages from when they are just 4 cells until they are a cluster of many cells about 5 days after fertilization</td>
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<tr>
<td>Chelsea &amp; Westminster Hospital R0150</td>
<td>To isolate human ES cells and to understand, at the molecular level, how ES cells are turned into specific types; To be able to predict reliably their ability to make appropriate amounts of tissues including nerve, bone, cartilage, muscle and lung after implantation</td>
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<tr>
<td>Birmingham Women's Hospital R0151</td>
<td>To undertake some of the initial studies of techniques such as nuclear transfer and parthenogenic activation</td>
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<tr>
<td>Newcastle Fertility Centre at Life R0152</td>
<td>To understand sperm trigger development during human fertilisation and what happens during the early cell divisions</td>
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*Source: Official website of the Human Fertilisation and Embryology Authority*
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<thead>
<tr>
<th>Hospital/Institute</th>
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<tbody>
<tr>
<td>Guys Hospital R0075</td>
<td>To improve methods for biopsy and preimplantation diagnosis of inherited genetic disease of human preimplantation embryos</td>
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<tr>
<td>Oxford Fertility Unit R0111</td>
<td>To investigate factors produced by the embryo and the endometrium (the lining of the uterus) which are necessary for successful implantation and to set up laboratory models to investigate the interactions between the embryo and endometrium during the implantation process</td>
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<tr>
<td>Guys Hospital R0133</td>
<td>To study the isolation and differentiation of neural and pancreatic islet progenitor cells from human ES cell cultures</td>
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<tr>
<td>Roslin Institute R0136</td>
<td>To develop enabling technologies for the treatment of degenerative diseases by the therapeutic replacement of cells, for safety testing of new medicines and treatments, and to create models for understanding disease</td>
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<tr>
<td>NURTURE - R0141</td>
<td>To focus on receptor systems in heart and smooth muscle cells formed from stem cells to assess the normality of their behavior</td>
</tr>
<tr>
<td>Princess Anne Hospital R0142</td>
<td>To examine the expression and regulation of genes that are likely to be susceptible to programming using sensitive molecular and microscopic procedures designed for early embryos</td>
</tr>
</tbody>
</table>

*Source: Official website of the Human Fertilisation and Embryology Authority*
Islet Transplantation in Seven Patients with Type 1 Diabetes Mellitus Using a Glucocorticoid-Free Immunosuppressive Regimen” The New England Journal of Medicine, July 27, 2000

“Clonal identification of multipotent precursors from adult mouse pancreas that generate neural & pancreatic lineages.” Nature Biotechnology, August 22, 2004


www.namiscc.org/newsletters/December01/SCI-stem-cell-research.htm


NIH Website

www.jci.org/cgi/content/full/113/10/1376

Economic impact of Calif. stem cell plan debated

By Deena Beasley and Leonard Anderson, Reuters

Analysis Group, Economic Impact Analysis, Proposition 71