REPORT TO GOVERNOR MALLOY
AND
THE GENERAL ASSEMBLY

AN ACT PERMITTING STEM CELL RESEARCH AND BANNING
THE CLONING OF HUMAN BEINGS

November, 2011

Connecticut Stem Cell Research Advisory Committee
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Report to Governor Malloy and the General Assembly
An Act Permitting Stem Cell Research and Banning the Cloning of Human Beings

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Public Act 05-149, “An Act Permitting Stem Cell Research and Banning the Cloning of Human Beings” (the Act), was approved by the Connecticut General Assembly and signed by Governor M. Jodi Rell on June 15, 2005. The Act made available up to $100 million dollars over a ten year period from the State’s Tobacco Settlement Fund to the Stem Cell Research Fund for the purpose of grants-in-aid for conducting embryonic or human adult stem cell research.

The Act required the Stem Cell Research Advisory Committee to report annually to the Governor and the General Assembly on: (1) the amount of grants-in-aid awarded to eligible institutions from the Stem Cell Research Fund pursuant to section 2 of the Act, (2) the recipients of such grants-in-aid, and (3) the current status of stem cell research in the State. Although this reporting requirement was eliminated in 2010, this report is provided electronically as an informational update on the stem cell program. This report covers the period from June 30, 2010 through July 31, 2011.

On July 19, 2011, the State allocated $9.80 million in grants-in-aid to researchers in Farmington, Storrs, and New Haven. Since passage of the enabling legislation in 2005, the State of Connecticut has allocated a total of $59.04 million in support of stem cell researchers. To date, State funding has provided the resources to fully or partially support 151 full or part-time positions at Yale University and 40 full time equivalents at the University of Connecticut. In addition, State funding supports the salaries of seven new positions at Wesleyan University. These highly skilled professionals represent a new breed of sophisticated work force in Connecticut, and are anticipated to have significant long-term impact on the State’s economic development.
I. INTRODUCTION AND BACKGROUND

Passage of the Act positioned Connecticut as the third state in the nation, behind only California and New Jersey, to provide public funding in support of embryonic and human adult stem cell research. It mandated the establishment of the Connecticut Stem Cell Research (SCR) Advisory and Peer Review Committees by October 1, 2005, and required the Commissioner of Public Health, as Chair of the Advisory Committee, to convene the first meeting by December 1, 2005.

Within the Department of Public Health (DPH), the Office of Research and Development was tasked with implementation of the Act for the State of Connecticut, including identifying and recruiting members to the Connecticut Stem Cell Research (SCR) Advisory and Peer Review Committees. Additionally, the Act designated Connecticut Innovations, Inc. (CI) as administrative staff of the SCR Advisory Committee, responsible for assisting in the development of the application for grants-in-aid, reviewing such applications and preparing and executing assistance agreements in connection with awarding the grants-in-aid.

II. COMMITTEE ACTIVITIES

The primary focus of the SCR Advisory and Peer Review Committees from July 1, 2010 to July 31, 2011 was issuance of a fifth Request for Proposal, receipt and review of 77 applications for grants-in-aid, and the allocation of available dollars. A new category of group grants was established with priority given to projects involving disease directed collaborative arrangements between industry (e.g., biotechnology and pharmaceutical companies), medical centers and academic institutions, with the intention of beginning Federal Food & Drug Administration review within four years of the awarding of the grant.

From February 2011 through May 2011, the Peer Review Committee completed the enormous task of rating and ranking each of the 77 applications for grants-in-aid from Connecticut’s research community. During a teleconferenced meeting on May 26, 2011, the SCR Peer Review Committee agreed as a body on the ratings and rankings of the proposals.

1 See Appendix A
2 See Appendix B
SCR Advisory Committee meetings were held on July 20, September 21, October 26, 2010, and on February 15, May 17, May 18, and July 19, 2011. The SCR Advisory Committee completed their review of applications and allocation of grants-in-aid during the meeting on July 19, 2011. All meetings were open to the public with notices and agendas on both the DPH and Secretary of State’s websites. Minutes and transcripts of meetings are also posted on the DPH website.

III. RECIPIENTS OF GRANTS-IN-AID

During the current period, the State of Connecticut awarded the following 20 grants-in-aid totaling $9.8 million to researchers in Farmington, Storrs and New Haven:

Identification of novel targets abnormally expressed in Prader-Willi Syndrome
University of Connecticut Health Center, Farmington, Kristin Martins-Taylor, Principal Investigator
$200,000

Regulation of mRNA stability and translation in pluripotent and differentiated hES cells
University of Connecticut Health Center, Farmington, Alissa Resch, Principal Investigator
$200,000

Single Cell Molecular Signatures for Hematopoietic Differentiation of Human Embryonic Stem Cells,
Yale University, New Haven, Rong Fan, Principal Investigator
$195,251

Role of Kalirin, a risk factor for schizophrenia, in human stem cells
University of Connecticut Health Center, Farmington, Xin-Ming Ma, Principal Investigator
$200,000

The Role of Endocardial Cells in Human Down Syndrome-Related Heart Defects
Yale University, New Haven, Peter Amos, Principal Investigator
$200,000

Role of the histone variant H2A.X in the establishment of the epigenetic landscape of human embryonic stem cells
Yale University, New Haven, Pascal Drane, Principal Investigator
$200,000

MicroRNA mediated derivation of hematopoietic stem cells from human embryonic stem cells
Yale University, New Haven, Shangqin Guo, Principal Investigator
$200,000

Investigation of gene expression adaptations to alcohol in iPS cell derived neural cultures from alcohol dependent control subjects
University of Connecticut Health Center, Farmington Jonathan Covault, Principal Investigator
$196,836
<table>
<thead>
<tr>
<th>Project Title</th>
<th>Institution</th>
<th>PI Name</th>
<th>Funding Amount</th>
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<tbody>
<tr>
<td>Identification and purification of smooth muscle cells from differentiating human embryonic stem cells for vascular tissue engineering</td>
<td>Yale University, New Haven</td>
<td>Sumati Sundaram</td>
<td>$200,000</td>
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<tr>
<td>Cytoplasmic dsRNA response in human embryonic stem cells</td>
<td>University of Connecticut Health Center, Farmington</td>
<td>Gordon Carmichael</td>
<td>$750,000</td>
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<tr>
<td>Devising a multidisciplinary approach for the treatment of articular cartilage damage using human ESC-derived chondrocytes</td>
<td>University of Connecticut Health Center, Farmington</td>
<td>Hicham Drissi</td>
<td>$650,000</td>
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<tr>
<td>Phosphorylation Dynamics of Pluripotent Stem Cells</td>
<td>University of Connecticut Health Center, Farmington</td>
<td>David Han</td>
<td>$570,000</td>
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<td>Pulsatile tissue-engineered grafts for surgical correction of single ventricle cardiac anomalies</td>
<td>Yale University, New Haven</td>
<td>Yibing Qyang</td>
<td>$375,000</td>
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<tr>
<td>Mechanisms of RNA Surveillance in Human Embryonic Stem Cells</td>
<td>Yale University, New Haven</td>
<td>Sandra Wolin</td>
<td>$750,000</td>
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<tr>
<td>Differentiation of human iPSC and ES into functional neurons</td>
<td>Yale University, New Haven</td>
<td>Flora Vaccarino</td>
<td>$744,464</td>
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<tr>
<td>Elucidating the development and disease of cortical motor neuron using human pluripotent stem cells</td>
<td>UConn Health Center, Farmington</td>
<td>Xue Jun Li</td>
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<td>Angiogenesis of Embryonic Stem Cell Derived Hippocampus Transplants</td>
<td>Wesleyan University, Middletown</td>
<td>Laura Grabel</td>
<td>$750,000</td>
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<tr>
<td>Development of a Potential Therapy for Osteoarthritic Cartilage Damage using hESC-derived Chondrogenic Cells</td>
<td>Chondrogenics, Inc., Farmington</td>
<td>Caroline Dealy</td>
<td>$1,290,499</td>
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<tr>
<td>Continued Operation and Expansion of the Human Embryonic Stem Cell Core Facilities at the Yale Stem Cell Center</td>
<td>Yale University, New Haven</td>
<td>Haifan Lin</td>
<td>$500,000</td>
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<td>Stem Cell Approaches for Defining Patient-specific Predisposition to Idiosyncratic Drug induced Liver Injury</td>
<td>University of Connecticut, Storrs</td>
<td>Urs Boelsterli</td>
<td>$1,290,499</td>
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**CONNECTICUT’S STEM CELL RESEARCH COMMUNITY**

Since passage of the enabling legislation in 2005, the State of Connecticut has allocated a total of $59.04 million in support of stem cell research at the University of Connecticut, Yale University, and Wesleyan University. The following describes the state of publicly funded stem cell research efforts at Yale University, Wesleyan University, and the
A. University of Connecticut Stem Cell Research

The University of Connecticut is dedicated to establishing an internationally recognized program focused on human embryonic stem cells and regenerative medicine. In collaboration with scientists at Yale and Wesleyan Universities, UCONN has developed state-of-the-art research programs aimed at bringing human stem cell therapies to patients. With support from our citizens and legislators, the grant awards from the State of Connecticut Stem Cell Fund support research in over 30 laboratories at the University of Connecticut. UCONN is also training the next generation of clinical and basic research scientists who will lead this new field of investigation into areas of medical practice and launch new Connecticut-based biotechnology companies.

Retreat

On October 27, 2010 the UConn Stem Cell Institute hosted a state wide stem cell research retreat. Connecticut funded investigators from UConn/UCHC, Yale and Wesleyan presented, discussed, and collaborated on ongoing research projects at this one-day symposium.

Major accomplishments:

1) The University of Connecticut Stem Cell core facility generated four human embryonic stem cell lines, CT1, CT2, CT3 and CT4, in the State of Connecticut, through the efforts of Drs Ge Lin and Ren-He Xu. These lines have been approved and are eligible for federally funded research in NIH Stem Cell Registry.

2) Scientists from the University of Connecticut Stem Cell Institute made exciting discoveries that were published in international scientific journals. Selected publications include:

Antic, Srdjan

Chamberlain, Stormy J

Carmichael, Gordon


**Dealy, Caroline**


**Book chapter:**


**Nishiyama, Akiko**


Komitova M, Serwanski DR, and Nishiyama A. NG2 cells are not a major source of reactive astrocytes in neocortical stab wound. GLIA 59:800-809, 2011.


Feng J, Mantesso A, De Bari C, Nishiyama A, Sharpe PT. Dual origin of mesenchymal stem cells contributing to organ growth and repair. Proc

**Rasmussen, Theodore**


**Shin, Dong-Guk**


**Xu, Ren-He**


**Nishiyama, Akiko**
Age-dependent changes in the astroglialogenic fate of NG2 cells (polydendrocytes). Symposium on Glial Biology in Medicine, University of Alabama at Birmingham, December 2010.

Age-dependent lineage plasticity of NG2 cells (polydendrocytes). Institute of Molecular Biology, University of Oregon, Eugene. April 2011.

**Public Media Coverage**
March 21, 2011. TV News (NBC30): Television segment on stem cell research and StemConn meeting.


covered work on hESC derived chondrocytes for cartilage repair and as a Connecticut biotechnology enterprise.


**Patents Filed:**

**Economic impact of State Stem Cell funding for UConn:**
The stem cell grant program has created and maintained employment for 40 full-time equivalents in 32 labs at the University.

We are expanding our Technology Incubation Program (TIP), with a new state-of-the-art incubator facility co-located with the UCHC Stem Cell Core Lab and other cell science departments. The facility will provide companies with wet lab space ranging from 300 SF to 1000 SF as well as business services. This strategic move assists in assuring that UConn will deliver on the commercial promise of the State’s investment to UConn stem cell research. Helping to provide resources to build new firms based upon our discoveries and recruit bioscience companies pursuing stem cell therapies, relocation at UCONN and collaboration with Connecticut researchers looking to advance commercialization will lead to further viability and success of businesses in the State of Connecticut.

Two Federal grants have been obtained through collaboration between the TIP and the UConn Stem Cell Institute which provides access to unique equipment that will further research of for both TIP firms as well as faculty researchers. This specialized equipment, aimed at advancing the speed and efficiency of this research, would be otherwise unattainable for fledgling start ups.

UCONN R&D Corp and the TIP have obtained the services of a bioscience business expert to review UCONN stem cell grants and match research activities underway with industry interests in the stem cell arena. A key component of this effort is to identify those research activities of keen interest to both large and small companies to seek industry partnerships as well as start up opportunities.

UCONN has an advanced infrastructure for technology commercialization that is modeled after national best practices and is designed to take research from the lab to the marketplace. The infrastructure not only offers business and technical expertise and support for faculty and UCONN affiliated start ups, it supports industry access to the University and encourages students and faculty to engage in commercialization of technology. The full scope of this infrastructure will be utilized to support commercialization of stem cell research at UCONN.

“Chondrogenics, Inc.” was formed in 2010 in collaboration with UConn Research & Development (UConn R&D) and the University of Connecticut Center for Science and Technology Commercialization (CSTC). The purpose of the company is to develop the commercialization potential of hESC and iPSC derived chondrogenic cells for future use in human therapies. Dr. Dealy is leading a collaborative effort between Chondrogenics and the University of Connecticut Health Center to develop the potential of a stem-cell based therapy for osteoarthritis.

Critical need for continued Connecticut Stem Cell funding:

The University of Connecticut has committed resources, equipment and space to establish its world-class human embryonic stem cell research program. These investments include:

A $52 million dollar, 117,000 square foot, research building in Farmington opened in July 2010 and is home to the Stem Cell Institute along with many of our top scientists. One half of this space houses the stem cell program with the remainder dedicated to state-of-the-art imaging and computing technologies along with the Technology Incubator Program.

An investment of over $1 million dollars to establish and equip the human embryonic stem cell (hESC) core facility. This core facility provides training, hESC lines and other services to researchers from all over the state of Connecticut. During the past year, our hESC core facility produced four human embryonic stem cell lines available for federally funded research. This achievement is a testimony to our core's high level of expertise and positions both the State of Connecticut and the University to be at the forefront of international stem cell research.

B. Yale University

The $23.4 million in funding that Yale received from the State since 2007 has transformed stem cell research at Yale—it has allowed Yale, for the first time, to build an infrastructure and a vibrant community of investigators to conduct stem cell research. Prior to the passage of Public Act 05-149, there was only one investigator at Yale working on human embryonic stem cells. Today, there are 66 laboratories on Yale campus actively pursuing stem cell research. Specifically, the initial funding of $7.3 million from the State in 2007 allowed Yale to build an infrastructure of core facilities, initiating new research projects, recruiting new faculty, and stimulating new collaborations both within the Yale community and throughout Connecticut. The additional $16.1 million in funding that Yale received from the State in 2008 through 2010 has further generated a synergistic effect with the current funding to enhance stem cell research in Connecticut. Thirteen new projects were awarded in 2010, eight to young investigators with interests in stem cell research and five to established investigators with interests in expanding their research into the stem cell research field. The access to human embryonic stem cell lines, imaging, genome sequencing, and data analysis technology at Yale’s core laboratories has paved the road for scientists to conduct their research.
1. Infrastructure of Core Facilities

The Yale Stem Cell Center (YSCC) moved into the new building on Amistad Street during the first week of August 2007. The YSCC established the following core laboratories, funded by a Core Facility grant from the Connecticut Stem Cell Research Fund (CSCRF). This Core grant allowed Yale to purchase major equipment and supplies, as well as salaries for some of the experts who manage the Cores.

a. **Human Embryonic Stem Cell (hESC) Core.** This Core, staffed by a Technical Director and a technician, serves as a storage, distribution, and training center for hESCs and develops new hESC technology for researchers in the State of Connecticut. In addition, it is an important research site for investigators who are extending their work to non-federally-approved hESC lines. The hESC Core staff has trained over 100 investigators from 30 labs on how to culture hESC and induced pluripotent stem cells (iPSCs) and is supplying hESC cell lines and is growing and differentiating cells (e.g., neurons and erythroid cells) for 24 labs.

b. **Confocal Microscope Core.** This Core provides state-of-the-art imaging for research on embryonic and adult stem cells. The equipment includes a Leica TCS SP5 AOPS Spectral Confocal Microscope equipped with a scanning stage. The Confocal Core lab was customized for this microscope and the equipment arrived in October 2007. This Core has been fully booked and provides service to 154 investigators from 36 labs.

c. **Fluorescence Analysis and Cell Sorting (FACS) Core.** The Yale School of Medicine purchased a BD FACSArgia cell sorter and a BDTM LSR II Cell Analyzer Special Order System. The FACS Core lab was customized for this equipment and the equipment arrived in September 2007. This Core complements the existing Core on the Medical School campus and between the two Cores they are providing service to over 800 investigators.

d. **Genomics Core.** This Core consists of an Illumina Genome Analyzer that is located on the second floor of the Amistad building. The Illumina Genome Analyzer, purchased in part with a Hybrid Grant from the CSCRF and with support from Yale, is staffed by a Technical Director who is responsible for the day-to-day operation and management of the Core. This technology is working at a >90% success rate. Data has been obtained for the stem cell research projects of 12 laboratories and some of the results have been published in top tier journals such as *Science*. This service is expected to propel both academic and industrial stem cell researchers in the State to the forefront of the genomic and genetic research of stem cells.

2. New Research Projects

1. **Dr. Angelique Bordey, Associate Professor, Departments of Neurosurgery and Cellular & Molecular Physiology and Physiology.** "Mechanical Control of Neural Stem Cell Fate." The Adult human brain has been revealed to possess its own stem cells and is more plastic than we could have ever dreamed. Using neural stem cells (NSCs) to restore damaged or dying neurons or glia and improve brain functions in the cases of neurodegenerative diseases, stroke, and even aging is
now plausible. However, the lack of markers of adult NSCs has significantly
impended progress towards understanding the biology of these cells and their use
for endogenous repair. In the adult human brain, NSCs reside in the
subventricular zone (SVZ) along the lateral ventricle and constitute a
subpopulation (~5%) of cells expressing glial fibrillary acidic protein (GFAP). Dr.
Bordey proposes to identify which of the GFAP-cells behave as NSCs and develop
approaches for studying them live in their microenvironment. Many cues in the
local tissue microenvironment regulate the commitment of stem cells to different
lineages. Dr. Bordey’s preliminary data suggest that a capillary constriction occurs
essentially in the SVZ (and not outside the neurogenic niche) and leads to
repetitive, transient mechanical stress in the NSC microenvironment. However,
the function of this mechanical stress is unknown. She is also planning to show
that mechanical cues experience in stem cell niche control the proliferation and
fate of stem cells through specific changes in their translational profile.

2. Dr. David Wells, Research Scientist, Department of Molecular, Cellular &
Developmental Biology. “Control of mRNA Translation in neuronal
Differentiation from hESC.” Human embryonic stem cells (hESCs) represent a
promising source of cells for replacement therapies for neurodegenerative
diseases. Understanding the pattern of gene expression that regulates the
differentiation of ESCs into a neuronal cell fate will be critical for the generation of
specific neuronal populations. For example, to treat Parkinson’s disease, one
proposed strategy is to use hESCs to generate dopaminergic neurons that could
then be transplanted into the basal ganglia. In order to safely and efficiently
differentiate hESCs into dopaminergic neurons, a detailed understanding of the
molecular signaling pathways controlling this process is required. Dr. Wells plans
to examine a mechanism that could control protein synthesis in this pathway and
thereby regulate differentiation of the neural cell fate. Protein synthesis is a
complex process that involves the transcription of specific genes (DNA) into
messenger RNA (mRNA) in the nucleus. The mRNA is then shuttled out of the
nucleus and translated into protein by ribosomes in the cell cytoplasm. What was
once thought to be a relatively cohesive flow of mRNA from the nucleus to the
ribosomes is now known to be regulated by mRNA binding proteins. Those mRNA
binding proteins in many cases sequester the mRNA from the ribosomes, keeping
the mRNA in a translationally dormant state, for synthesis upon cellular
stimulation. This type of mRNA regulation can have significant effects on cell
function—for example, it can target mRNA to one region of the cell so that protein
expression is realized in a distinct sub-domain of the cell. This process has also
been shown to play critical roles in both germ cell proliferation and in mature
neuron function. Dr. Wells plans to examine the role of a specific mRNA binding
protein that he believes has unique qualities to regulate hESC maintenance and
differentiation to CNS progenitors and ultimately into neurons.

3. Dr. Ee-Chun Cheng, Postdoctoral Associate, Department of Cell Biology. “The
Role of Epigenetic Factor-HP1 in Regulating hESC Pluripotency and
Differentiation.” Emerging data point to a key role for epigenetic mechanism in
 embryonic stem cell (ESC) self-renewal, pluripotency, and lineage-specific
differentiation. Each cell in the adult body contains exactly the same DNA (the
same genome). The difference between distinct cell types lies in the particular
subset of genes which are active (i.e., “expressed”) in a given cell or tissue. In
the nucleus of eukaryotic cells, DNA is extensively folded and compacted with different types of proteins, thus forming a dynamic structure called chromatin. Diverse biochemical modifications of chromatin occur during development. These modifications, called epigenetic modifications, are known to profoundly regulate gene expression patterns. Recent studies suggest that as cells develop towards specific fates, regions of their genome are ‘closed-down’ by various epigenetic modifications. That is, as distinct areas of a cell’s genome are shut down, their developmental potential becomes increasingly limited. Deciphering the nature of these epigenetic instructions in ESCs will have important implications for their future therapeutic use. Dr. Cheng proposes to study the role of a key epigenetic factor, Heterochromatin protein 1 (HP1), in regulating hESC self-renewal and differentiation. HP1 is one of the most fundamental chromatin-associated proteins. It is well known that HP1 is essential for gene silencing throughout evolution and has an important role in human cells. We hypothesize that HP1 silences a variety of differentiation promoting genes in hESCs, thereby maintaining pluripotency. If this is true, loss of HP1 would destabilize the fate of hESCs in a fundamental way. Therefore, we will test if disrupting HP1 activity in hESC leads to defects in self-renewal and, further, if such disruption results in cellular differentiation (i.e., loss of pluripotency). Also, since HP1 is an epigenetic factor and can conceivably affect many regions of the genome, Dr. Cheng will conduct high-resolution whole-genome mapping in hESCs to determine precisely which genes are bound by HP1 and how their expressions are affected by such interaction. Finally, since HP1 also brings other chromatin modifiers or transcriptional repressors to the genome, Dr. Cheng will perform co-immunoprecipitation assays to isolate molecular complexes containing HP1, and identify unknown members within these complexes. If the above-proposed aims are achieved, this study will further our understanding of epigenetic regulation of stem cell self-renewal and open a new territory for hESC research. Moreover, since a reduction in levels of HP1 family members is correlated to certain cancers, this study may also provide a novel insight into oncogenesis and its relation to stem cell biology.

4. Dr. Chunsheng Dong, Postdoctoral Associate, Department of Cell Biology. “Efficient Gene Targeting in hESCs via Recombineering Based Long Arm Targeting Vector.” hESCs have the properties of self-renewal and pluripotency and present an excellent model to understand the molecular mechanisms of mammalian early development. Gene targeting is one of the key approaches to study the function of individual genes. In the mouse genome, thousands of genes have been knocked out and analyzed in vivo over the past 20 years. However, hESCs cannot be used to study mutations in vivo. Thus gene targeting in hESCs is a valuable approach to reveal gene function in vitro. Unlike mouse embryonic stem cells, hESCs are not easily amenable to efficient gene targeting as some groups have reported, which make this approach a challenging and laborious process in hESCs. The chief reasons include a low recombination frequency as well as a cloning efficiency. It has clearly been shown by some groups that the frequency of homolog recombination increased dramatically after increasing the homolog arms of the targeting vector. The traditional way to construct targeting vector is laborious work since one has to find appropriate restriction digestion strategies to put together usually six to seven DNA fragments. Dr. Dong seeks to develop a more efficient way to generate long homolog arm (about 10k)
targeting vector based on recombineering in E. coli. He also plans to improve the method of targeting vector delivery in hESCs as well as the cloning efficiency. His goal is to set up a platform for highly efficient gene targeting in hESCs.

5. Dr. Richard Flavell, Sterling Professor and Chairman, Department of Immunobiology; Investigator, Howard Hughes Medical Institute. “Reconstitution of Human Hematopoietic System by HSCs Derived from Human Embryonic Stem Cells in Humanized Mice.” Dr. Flavell’s laboratory has developed a powerful system for the humanization of the immune system of mice. In brief, this involves engraftment of newborn mice with hematopoietic stem cells (HSC) of human origin. In the original model, HSC from a variety of human sources have been shown to successfully engraft these mice including HSC from cord blood and fetal liver. A major limitation of this system is a source of hematopoietic cells. Further, it would be highly desirable to be able to match hematopoietic cells derived from a given human source with other tissue from that same source. Human ES cells provide a unique opportunity to generate HSC as well as other tissue and to repopulate the mouse in this way.

Engraftment of HSC in mice is still problematic and for that reason we have genetically modified mice at several loci to generate a unique recipient mouse which provides human factors which improve mouse engraftment by human HSC. In brief these factors include human cytokines, major histocompatibility complex molecules and other molecules that facilitate engraftment. However, a severe limitation of the utilization of this much improved mouse model is a source of human HSC of the kind listed above. Dr. Flavell proposes to derive human HSC from human ES cells, to characterize these for their purity and stem cell capability and to engraft them into the genetically modified mice. Such engrafted mice will then be characterized for the efficiency of engraftment, fidelity of the lineages obtained and functionality of the cells.

6. Dr. Xin Quan Ge, Postdoctoral Associate, Department of Cell Biology. “The Role of dormant Replication Origins in Ensuring Genome Integrity in hESCs.” Maintenance of genome integrity is especially important for stem cells, as long-lived multicellular organisms depend on tissue replenishment of small pools of stem cells that must be self-renewed and maintained with a minimum of mutations throughout life. To ensure genome integrity, DNA must be replicated accurately and completely during S phase of the cell cycle. DNA replication initiates from numerous starting sites, so-called replication origins. Origins are licensed in large excess prior to DNA replication. When cells enter S phase, only a small subset of licensed origins are activated to initiate replication forks, leaving the rest to become dormant origins. Recently Dr. Ge has demonstrated that when primary replication forks are slowed or stalled, these dormant origins can initiate additional replication forks to promote complete genome replication. Without dormant origins, prolonged replication fork stalling will elicit for collapse and chromosome recombination, which can result in genome rearrangement. Consistent with this idea, cultured human cells, C. elegans and mice partially depleted of dormant origins display significantly reduced survival when under replication stress. Furthermore, reducing dormant origins in mice by knocking down one of the licensing proteins resulted in stem cell deficiency and premature aging in mice. Therefore Dr. Ge hypothesizes that the use of dormant origin is a
particularly important mechanism to ensure genome stability in stem cells. Due to the importance of genetic stability in hESCs, particularly if they are to be used for medical applications, Dr. Ge proposes to investigate the usage of dormant origins in hESCs and determine their role in maintaining hESCs genome integrity. As a comparison, she will also study dormant origins on cells at different stages during differentiation from hESCs into neural and hematopoietic lineages. To carry out this project, she will first study the overall process of origin licensing and DNA replication in hESCs during their differentiation. This serves as a basis for her experiments at the next step where she will specifically compare dormant origin usage in hESCs and their derivative neural progenitor cells (NPC) and hematopoietic stem cells (HSC) when they are under replication stress. Based on her preliminary data on mouse ES cells, she expects hESCs employ dormant origins at high efficiency. Then she will determine the importance of dormant origin firing in maintaining genome stability in hESCs and their derivative NPCs and HSCs by experimentally modulating the number of licensed dormant origins and then examining the effect this has on the ability of cells to survive replication stress. In addition, she will investigate other possible mechanisms that contribute to hESCs genome stability such as DNA damage checkpoint and DNA repair. This will allow her to gain a systematic understanding of how hESCs maintain genome integrity. Finally, she will determine the requirement of dormant origins during hESCs self-renewal and differentiation into various lineages. These experiments will reveal the physiological significance of dormant origins and dissect their differential requirement during hESCs self-renewal and differentiation.

7. Dr. Lawrence Rizzolo, Associate Professor, Departments of Anatomy, Experimental Surgery, and Ophthalmology. “Co-differentiation of hESC-derived Retinal and Retinal Pigment Epithelial Progenitors.” Many retinal diseases involve the retinal pigment epithelium (RPE) and its function as the outer blood-retinal barrier, either as a primary cause or a secondary consequence. The techniques for transplanting RPE and retinal cells are well established, but RPE transplantation usually fails, because the transplanted cells are not fully functional. Dr. Rizzolo is interested in knowing more about how to produce the best cells for transplantation. He is investigating hESCs as a source of RPE and retinal cells, and how to promote their maturation in culture in a way that improves their success in transplants. The investigation of the maturation process in culture may also lead to medical therapies that avoid transplantation altogether.

8. Dr. Erik Shapiro, Assistant Professor, Departments of Diagnostic Radiology and Biomedical Engineering. “In Vivo Evaluation of hESC, iPSC, and Adult Brain Derived neural Progenitor Cell Transplantation and Migration using MRI.” Human neural progenitor cells show tremendous promise in the treatment of central nervous system disease, in both cell supportive and cell replacement strategies. These cells can now be generated from adult human brain tissue, hESCs, and induced pluripotent stem (iPS) cells. It is unclear what effect cell origins has on neural progenitors generated in these different ways. In this work, Dr. Shapiro and his co-investigator, Dr. Eleni Markakis, will undertake the first comparative studies aimed at characterizing cells generated from these three sources and evaluate their suitability for use in vivo. Using methodologies honed in their previous CT Stem Cell Seed grants, they will establish optimal growth/proliferation conditions for cells of adult, hESC, and iPSC origins, establish
their limits of proliferation, optimize growth arrest and differentiation paradigms in vitro, and study cell migration characteristics in vivo for cells of all three origins.

9. Dr. Eun Jung Lee, Associate Research Scientist, Department of Anesthesiology. “Maturation of hESC-derived Cardiomyocytes In Vitro using 3D Engineered Tissue Model System.” As one of the limitations currently with hESC-derived cardiomyocytes is their embryonic phenotype based on their size, organization and electric properties in 2D culture, it is essential to better understand the microenvironmental cues that regulate differentiation and maturation of hESC-derived cardiomyocytes for advancement in stem cell-based therapy. Traditional 2D cultures are not physiologic and the lack of mechanical stimulation and biological cues from other cell types may be the causes of immature cardiomyocytes as cardiomyocytes exist in an environment with extreme dynamic changes of stress and strain. Therefore, Dr. Lee’s proposal describes using unique 3D engineered tissue systems incorporating mechanical stimulation such as mechanical stretching and shear stress to evaluate hESC-derived cardiomyocyte maturation in vitro. The innovation of this proposal primarily relates to a novel approach for evaluating hESC-derived cardiomyocytes function in vitro, using two custom-designed 3D engineered cardiac tissue models. First is the engineered cardiac chamber that allows the direct assessment of cardiomyocyte functionality, force generation, and pressure-volume loops, and is completely novel in its design. Second is the novel perfusion system that allows the culture of various cell types in the presence of a bulk flow field, which is also, to the best of our knowledge, the first demonstration of in vitro perfusion of a gel-based system to study the impact of fluid flow on cell growth, remodeling and microvascular formation. These engineered tissues represent a more realistic model of a natural ventricle than traditional 2D planar cell cultures or 3D scaffolds, yet provide a more precise level of experimental control than animal or patient studies, and allow long-term cultivation in vitro. The ability to study human cardiac cell differentiation in 3D engineered tissue offering physiologic environment with mechanical cues will not only help to elucidate mechanisms on how cardiomyocytes mature, which is not possible with 2D cultures or in vivo, but also will greatly advance developing strategies for cardiac repair as this may help to elucidate how new myocardial cells can properly integrate into the adult myocardium followed by the cell-therapy.

10. Dr. Efrat Oron, Postdoctoral Associate, Department of Cell Biology. “Molecular Mechanisms of Germ Layer Induction in hESCs.” The ability of embryonic stem (ES) cells to grow in culture and give rise to diverse cell lineages can be exploited to produce specific cell types for medicine and research. Differentiation of ES cells is a multi-step process which begins with the induction of primary germ layers – ectoderm, endoderm and mesoderm. Very little data regarding this process is currently available and the key molecular components that control first steps of differentiation remain unidentified. Consequently, it has been difficult to faithfully recapitulate sequential steps of lineage specification in tissue culture. Dr. Oron is working to decipher the molecular mechanisms guiding germ layer induction. To do this, she proposes to use an in vitro ES differentiation system combined with a functional genomics approach. First, she will use high-throughput sequencing to generate accurate and sensitive transcription profiles of hESCs
undergoing embryoid body differentiation. Bioinformatics tools will be used to analyze the data and select genes that are expressed prior to and during the emergency of germ layers and likely regulate ES cell differentiation. Next, we will down-regulate the selected genes using shRNAs and evaluate the potential of shRNA-targeted ES cells to give rise to primary germ layers. Finally, positive hits will be further tested using direct differentiation assays. These studies are critical for obtaining a better understanding of how different cell lineages can be generated from ES cells. The discoveries made could lead to novel therapeutic approaches to repair tissues damaged by injury or disease.

11. Dr. Matthew Rodeheffer, Assistant Professor, Departments of Comparative Medicine and Molecular, Cellular and Developmental Biology. “Identification and Characterization of Multipotent Cell Populations from Human Adipose Tissue for Application in Regenerative Therapies.” The field of regenerative medicine aims to develop protocols for therapeutic replacement of damaged or diseased tissues or organs by tissue engineering, stem cell therapy, or other approaches. Adult-derived stem cells are a conceptually attractive tool for regenerative medicine and tissue engineering due to the potential of generating replacement tissues from the recipient’s own cells, eliminating the possibility of rejection. Of the tissues being considered as a source for adult-derived stem cells, adipose tissue is one of the most promising, due to the abundance of available tissue and the relative ease of tissue isolation. Adult-derived stem cells that are capable of limited differentiation into several cell types in cell culture have been isolated from unfractionated adipose tissue. However, human adipose tissue contains many different cell types – including preadipocytes, endothelial cells and immune cells – whose specific potential for use in regenerative medicine remain poorly characterized. Dr. Rodeheffer hypothesizes that human adipose tissue harbors distinct multipotent cell populations that will provide improved starting material for tissue engineering. He proposes two objectives to investigate the functions of distinct cell subpopulations from human adipose tissue. For the first he will isolate different subpopulations of cells from human adipose tissue based on differential expression of cell surface makers, as determined by fluorescence-activated cell sorting, and determine their ability to become bone, cartilage, muscle and fat cells in culture. The second will test the hypothesis that these distinct multipotent cell populations will provide better starting material for regenerative medicine by testing the ability of these cell populations to form adipose tissue in vivo. These studies will provide the nucleus for future proposals and collaborations to establish the full potential of adipose tissue-derived cells in regenerative medicine in a range of applications, from recovery of heart function after a heart attack to generation of bioengineering of replacement blood vessels or fat tissue for use in reconstructive surgery.

12. Dr. Caihong Qiu, Associate Research Scientist, Department of Cell Biology. “Regulation of Lin28 in hESC Self-renewal and Differentiation.” Dr. Qiu is investigating the interaction of pluripotent factors to maintain hESCs at their continuously renewing state and not proceeding to more specialized cell types. She will specifically emphasize the mechanistic study on how Lin28 positively regulates the Oct4 expression at the translational level, and how Oct4 stimulates the Lin28 expression. Oct4 is a key component of molecular circuitry in regulating hESC growth and keeping their own property. Lin28 is abundantly expressed in
hESCs and directly regulates Oct4 gene expression, and should play an important role in keeping hESCs in their unlimited growth and the ability to form other mature cell types. Also both Oct4 and Lin28 are among the four factors used to convert fibroblasts both molecularly and morphologically into hESC-like cells, called induced pluripotent stem cells (iPSCs). The investigation of the mechanistic interaction between Oct4 and Lin28 will further illustrate the detailed progression of converting fibroblasts to iPSCs, and their characteristics of hESCs and iPSCs. It will harness the clinical applications of hESCs and iPSCs.

Dr. Qiu will also investigate the biological function of Lin28 in the process of hESCs renewing themselves and changing themselves into other specific cell types. She will work on identifying the new targets regulated by Lin28 in hESCs. She will further explore the roles Lin28 will have a high impact on the therapeutic potential of hESCs and iPSCs. The success of her studies will add another layer of mechanistic understanding of hESC intra-regulation by translation.

Dr. Diane Krause, Professor, Departments of Laboratory Medicine, Pathology, and Cell Biology. “Use of hESCs and iPSCs to Study Megakaryoblastic Leukemia.” The long-term goals of Dr. Krause’s research are to determine how infantile leukemia develops. Some children are born with or diagnosed with leukemia within the first few months of life. In these children, the leukemia actually begins while the baby is still in utero from a population of blood stem cells that is no longer present in the same form after birth. Therefore, in order to study this leukemia, she proposes to use hESCs, which recapitulate this early fetal stage of blood development. Specifically she will modulate these blood progenitors in order to determine how they become leukemia cells. In addition to helping to develop improved treatments for infantile leukemia, this work will also elucidate much about normal fetal and adult blood cell development, which can help to guide the development of novel therapies for adult leukemia and other blood diseases that cause hemorrhage, anemia, and infection.

3. Recruitment of Leading Stem Cell Researchers

The State stem cell funding has aided Yale’s ability to recruit eleven faculty members to the Yale Stem Cell Center. These include:

- Caihong Qiu, PhD, Albert Einstein College of Medicine (2007)
- Natalia Ivanova, PhD, Princeton University (2008)
- Jun Lu, PhD, Broad Institute of MIT and Harvard (2009)
- Shangqin Guo, PhD, Harvard University (2009)
- Valentina Greco, Ph.D., Rockefeller University (2009)
- Yibing Qyang, PhD, MGH, Harvard Stem Cell Institute (2009)
- Valerie Horsley, PhD, Rockefeller University (2009)
- Matthew Rodeheffer, PhD, Rockefeller University (2009)
- In-Hyun Park, Ph.D., Children’s Hospital, Harvard Medical School (2009)
- Andrew Xiao, Ph.D., Rockefeller University (2010)

The State stem cell funding played a critical role in Yale’s winning these faculty members over other competitive institutions such as Harvard University and prominent universities in New York and New Jersey. In addition, 33 high level non-faculty researchers have
been supported with CT funds in the past three years and together these individual represent some of the best stem cell researchers in the world.

4. Collaborations within Yale and throughout Connecticut

The funding from the State to develop the Yale hESC Core Facility has given the YSCC the ability to provide hESC lines to investigators. This has stimulated a number of collaborative stem cell research projects. The majority of the investigators who received funding from the 2008, 2009 and 2010 CSCRF will use hESC lines from the hESC Core Facility and rely on the expertise of Dr. Qiu, who was recruited to the YSCC in 2007 as the director of the Facility, for guidance on the use of these lines.

Yale’s relationship with UConn, Wesleyan, the Department of Public Health, and Connecticut United for Research Excellence (CURE) has flourished as they work together to build the stem cell research base in the State. Examples of these forums and collaborations include the following:

a. **October 8, 2010:** New England Stem Cell Consortium (NESCC) Second Annual Junior Investigator Symposium. As members of the NESCC, University of Connecticut, Wesleyan University, and Yale organized and participated in this symposium targeted at graduate students and postdoctoral associates interested in stem cell research. It was attended by over 100 participants from New England.

b. **October 22, 2010:** Yale Stem Cell Center Third Annual Retreat. Keynote Speaker: Dr. Ihor Lemischka, Director of the Black Family Stem Cell Institute and Lillian and Henry M. Stratton Professorial Chair of Gene and Cell Medicine, Mount Sinai. This Retreat was attended by over 250 Yale faculty, staff, and students and members of the CT Stem Cell Research Advisory Committee. In addition to oral presentations by Yale faculty members, it also included a poster session with 16 posters from students and postdoctoral fellows. All of these activities are crucial for fostering a new generation of scientists who are enthusiastic about stem cell research.

c. **October 27, 2010:** Connecticut Stem Cell Research Retreat at the University of Connecticut Stem Cell Institute. The Program included seven talks from University of Connecticut, Wesleyan, and Yale faculty, updates on the Yale and Uconn/Wesleyan Cores, and a presentation on “The Current Legal Status of NIH Funding for hESC Research.” It was attended by staff from Connecticut Innovation, the Connecticut Department of Public Health, and University of Connecticut, University of Connecticut Health Center, Wesleyan, and Yale faculty, students, and staff.

d. **November 8, 2010:** New Horizons in Science meeting, a national meeting for science writers hosted at Yale University. The Yale Stem Cell Center provided a description of the stem cell research and facilities at the Center and provided a tour for the writers. The (CURE) arranged for the tours to showcase the New Haven biotech cluster and the stem cell research at Yale.

Additional collaborations with pharmaceutical and biotech industries are also evolving. The senior management of corporations such as BD Biosciences, Medtronic, Pfeifer, Novartis, Alnylam Pharmaceuticals, Polaris Ventures, RainDance Technologies Inc., etc. have visited and/or contacted the YSCC to express their interest in collaborating with the
YSCC. These partnerships will potentially create many opportunities for Yale to help establish a stem cell industry in the State. Yale Stem Cell Center is also a lead participant of the Northeast Stem Cell Consortium—an organization that promotes interaction and collaborations among 7 universities in the Northeastern United States (Harvard, UConn, Univ. of Maine, Univ. of Massachusetts, Univ. of Vermont, Wesleyan and Yale), affirming the leading position of Connecticut in stem cell research.

5. Economic Impact on the State of Connecticut

This funding has effectively leveraged other resources to boost the state economy. At Yale, over 75% of the state funds received to date, after initial investment in equipment, has been used for salary support, and has created 151 full-time and part-time positions in Connecticut. Moreover, this funding allowed us to attract more than $40M of research support from Yale and $7.65M research funds from outside the state, and this number is rapidly growing. These resources continue to generate more jobs and to develop our State’s competitive edge in economic development.

6. International Standing:

Yale Stem Cell Center, despite its young age, has gained a strong international reputation as a leader in stem cell research. For example, at the 2011 Annual Meeting of the International Society for Stem cell Research (ISSCR), which is the highest level and more comprehensive meeting representing the best science in the stem cell field, Yale showed strong representation. Out of 63 invited speakers, 35 were from the USA, and three were from Yale. In addition, two more Yale speakers were selected from abstracts competition.

C. Wesleyan University

A. Core Facility

Wesleyan University was a co-recipient with UConn of the grant-in-aid to establish a core facility in Farmington. Dr. Laura Grabel is Co-Principal Investigator along with Dr. Ren-He Xu. As reported under the University of Connecticut update on the core facility, the facility was successful in designing, establishing and providing training sessions for members of research teams from across the State of Connecticut. Dr. Grabel continued to run the outreach seminar program, with six seminars given at Connecticut colleges and universities, some institutions not visited previously, this past year. In addition, we began more extensive outreach to the general public, with talks at a library and arts center. Funds also supported Connecticut Stem Cell Research Retreats, at which researchers share their initiative-funded data and core facilities report updates. This past year, the third hands-on human embryonic stem cell workshop for undergraduates was held at Wesleyan University.

B. Research Projects

Directing production and functional integration of embryonic stem cell-derived neural stem cells Investigator, Investigator: Laura Grabel, PhD. In the third year of funding we continue to make progress. The goal of this project is to understand the conditions that promote neurogenesis of embryonic stem cells, in vitro and after transplant to the brain. Under Objective 1, using the human ESC lines H9 and H1 and a rapid, direct protocol for
generating neural stem cells we reported last year, we are now characterizing these cells further and examining the effect of growth factors and signaling molecules on their pattern of differentiation. We have also generated, in collaboration with Alex Lichtler at UConn Health Center, a derivative of H9 that expresses a lentiviral vector encoding a constitutive reporter as well as a neural stem cell reporter. Under Objective 2, we continue to study the fate of ESC-derived neural stem cells transplanted to the hippocampus. Recent analysis reveals a gradual decline in stem cell markers and increase in neuron-specific markers. We have also completed our analysis of the role of SDF-1a in the migration of transplanted ESC-derived NSCs in the dentate gyrus and have quantitative data that suggest this chemokine helps direct transplanted dispersal. We continue to work with FACS isolated forebrain progenitors derived from human ESCs and are using a line expressing an Nkx2.1 reporter. Transplants into control and pilocarpine seizure-experiencing mice are currently under way. A number of chapters and reviews have now appeared or are in press. We published a manuscript on the role of SDF-1 (CXCL12) in transplant migration (in PLoS One Biology) and another manuscript characterizing the GABAergic neurons generated from our transplants is currently under review. We have also submitted a manuscript that documents teratocarcinoma formation following transplantation of mouse ESC-derived neural progenitors to the hippocampus. We published a review on ESC neurogenesis (Journal of Cellular Biochemistry) and are working on a review on ESC-based transplantation covering biology and ethics.

Brain grafts of GABAergic neuron precursors derived from human and mouse ES cells for treating epilepsy, Investigator: Janice Naegele, PhD. The goal of this project is to generate inhibitory interneurons from ES cells and transplant them into sites of damage in a mouse model of temporal lobe epilepsy. The hope is that these neurons will dampen the hyperactivity that leads to recurring seizures. In the first year of funding we have established a long-term video/EEG recording system that accurately measures clusters of recurring seizures in pilocarpine-treated mice. Cell protocols are now in use that enrich for GABAergic neurons, and these cells are being transplanted to the dentate gyrus of treated mice. Preliminary results, including patch clamp analysis, suggest these cells are able to generate interneurons in the hippocampus and ongoing studies will determine their effect on the severity and frequency of seizures. A manuscript characterizing the GABAergic neurons generated from mouse ESC transplants in a chronic seizure model is currently under review. We have also made significant progress generating GABAergic progenitors from human ESCs using enrichment protocols and an Nkx2.1 reporter. Publications in the past year include several reviews and chapters on cell-based therapies for epilepsy.

C. Internal and External Collaborations

Laura Grabel/Janice Naegele/Gloster Aaron: The ongoing collaboration between these three Wesleyan University colleagues continues to be an integral and essential component of our projects. Grabel provides the ES cell expertise, Naegele the experience with epilepsy models, and Aaron the background in neurophysiology essential to test the function of transplanted cells. New contributions include the use of EEG recordings to measure seizure activity and use of the pilocarpine mouse model, which results in recurring seizures.

Human Embryonic Stem Cell Core at the University of Connecticut Health Center: This interaction provides us with needed support to grow and differentiate human ESCs and has proven invaluable.
Leonardo Aquilla and the Health Center FACS facility: We are routinely using this FACS facility for key experiments. Flow cytometric analysis has been key to characterizing the role of Hh in NSC survival. FACS isolation of Sox1-GFP+ cells is essential to our ongoing investigation of the how to remove teratocarcinoma-forming potential from the cell population prior to transplant. FACS isolation of human ESC-derived NSCs is currently underway.

Alexander Lichtler and the Health Center Vector Facility. This collaboration facilitated the isolation of the Sox1-GFP/ubiquitin-RFP mouse ESC line described above and will continue to contribute to our transplant work with the human lines. Construction of reporter vectors for our human ESC work is ongoing.

D. Economic Impact

Funding supports the salaries of three graduate students and two technicians, as well as a postdoctoral fellow. In addition, new internal and external support, based upon these projects, has led to hiring an additional technician. These projects have created seven new positions.

V. SUMMARY

Since 2005, the State of Connecticut has allocated a total of $59.04 million in support of embryonic stem cell researchers at UCONN, Yale, Wesleyan and the private sector. The allocation of funds has provided ongoing support to the development of two core stem cell research facilities, allowed for the recruitment and retention of world class researchers, supported new research efforts from established and junior faculty members at the University of Connecticut, Yale University, and Wesleyan University and is supporting important international and national research collaborations. This funding is also stimulating the advancement of exciting and innovative biotechnology economic development.
APPENDIX A

Public Act 05-149

AN ACT PERMITTING STEM CELL RESEARCH AND BANNING THE CLONING OF HUMAN BEINGS
Substitute Senate Bill No. 934
Public Act No. 05-149

AN ACT PERMITTING STEM CELL RESEARCH AND BANNING THE CLONING OF HUMAN BEINGS.

Be it enacted by the Senate and House of Representatives in General Assembly convened:

Section 1. (NEW) (Effective from passage) (a) As used in sections 1 to 4, inclusive, of this act and section 4-28e of the general statutes, as amended by this act:

(1) "Institutional review committee" means the local institutional review committee specified in 21 USC 360j(g)(3)(A)(i), as amended from time to time, and, when applicable, an institutional review board established in accordance with the requirements of 45 CFR 46, Subpart A, as amended from time to time.

(2) "Cloning of a human being" means inducing or permitting a replicate of a living human being's complete set of genetic material to develop after gastrulation commences.

(3) "Gastrulation" means the process immediately following the blastula state when the hollow ball of cells representing the early embryo undergoes a complex and coordinated series of movements that results in the formation of the three primary germ layers, the ectoderm, mesoderm and endoderm.

(4) "Embryonic stem cells" means cells created through the joining of a human egg and sperm or through nuclear transfer that are sufficiently undifferentiated such that they cannot be identified as components of any specialized cell type.

(5) "Nuclear transfer" means the replacement of the nucleus of a human egg with a nucleus from another human cell.

(6) "Eligible institution" means (A) a nonprofit, tax-exempt academic institution of higher education, (B) a hospital that conducts biomedical research, or (C) any entity that conducts biomedical research or embryonic or human adult stem cell research.
(b) No person shall knowingly (1) engage or assist, directly or indirectly, in the cloning of a human being, (2) implant human embryos created by nuclear transfer into a uterus or a device similar to a uterus, or (3) facilitate human reproduction through clinical or other use of human embryos created by nuclear transfer. Any person who violates the provisions of this subsection shall be fined not more than one hundred thousand dollars or imprisoned not more than ten years, or both. Each violation of this subsection shall be a separate and distinct offense.

(c) (1) A physician or other health care provider who is treating a patient for infertility shall provide the patient with timely, relevant and appropriate information sufficient to allow that person to make an informed and voluntary choice regarding the disposition of any embryos or embryonic stem cells remaining following an infertility treatment.

(2) A patient to whom information is provided pursuant to subdivision (1) of this subsection shall be presented with the option of storing, donating to another person, donating for research purposes, or otherwise disposing of any unused embryos or embryonic stem cells.

(3) A person who elects to donate for stem cell research purposes any human embryos or embryonic stem cells remaining after receiving infertility treatment, or unfertilized human eggs or human sperm shall provide written consent for that donation and shall not receive direct or indirect payment for such human embryos, embryonic stem cells, unfertilized human eggs or human sperm.

(4) Any person who violates the provisions of this subsection shall be fined not more than fifty thousand dollars or imprisoned not more than five years, or both. Each violation of this subsection shall be a separate and distinct offense.

(d) A person may conduct research involving embryonic stem cells, provided (1) the research is conducted with full consideration for the ethical and medical implications of such research, (2) the research is conducted before gastrulation occurs, (3) prior to conducting such research, the person provides to the Commissioner of Public Health documentation verifying that any human embryos, embryonic stem cells, unfertilized human eggs or human sperm used in such research have been donated voluntarily in accordance with the provisions of subsection (c) of this section, on a form and in the manner prescribed by the Commissioner of Public Health, (4) the general research program under which such research is conducted is reviewed and approved by an institutional review committee, as required under federal law, and (5) the specific protocol used to derive stem cells from an embryo is reviewed and approved by an institutional review committee.

(e) The Commissioner of Public Health shall enforce the provisions of this section and may adopt regulations, in accordance with the provisions of chapter 54 of the general statutes, relating to the administration and enforcement of this section. The commissioner may request the Attorney General to petition the Superior Court for such order as may be appropriate to enforce the provisions of this section.
Sec. 2. (NEW) (Effective from passage) (a) There is established the "Stem Cell Research Fund" which shall be a separate, nonlapsing account within the General Fund. The fund may contain any moneys required or permitted by law to be deposited in the fund and any funds received from any public or private contributions, gifts, grants, donations, bequests or devises to the fund. The Commissioner of Public Health may make grants-in-aid from the fund in accordance with the provisions of subsection (b) of this section.

(b) Not later than June 30, 2006, the Stem Cell Research Advisory Committee established pursuant to section 3 of this act shall develop an application for grants-in-aid under this section for the purpose of conducting embryonic or human adult stem cell research and may receive applications from eligible institutions for such grants-in-aid on and after said date. The Stem Cell Research Advisory Committee shall require any applicant for a grant-in-aid under this section to conduct stem cell research to submit (1) a complete description of the applicant's organization, (2) the applicant's plans for stem cell research and proposed funding for such research from sources other than the state of Connecticut, and (3) proposed arrangements concerning financial benefits to the state of Connecticut as a result of any patent, royalty payment or similar rights developing from any stem cell research made possible by the awarding of such grant-in-aid. Said committee shall direct the Commissioner of Public Health with respect to the awarding of such grants-in-aid after considering recommendations from the Stem Cell Research Peer Review Committee established pursuant to section 4 of this act.

(c) Commencing with the fiscal year ending June 30, 2006, and for each of the nine consecutive fiscal years thereafter, until the fiscal year ending June 30, 2015, not less than ten million dollars shall be available from the Stem Cell Research Fund for grants-in-aid to eligible institutions for the purpose of conducting embryonic or human adult stem cell research, as directed by the Stem Cell Research Advisory Committee established pursuant to section 3 of this act. Any balance of such amount not used for such grants-in-aid during a fiscal year shall be carried forward for the fiscal year next succeeding for such grants-in-aid.

Sec. 3. (NEW) (Effective from passage) (a) There is established a Stem Cell Research Advisory Committee. The committee shall consist of the Commissioner of Public Health and eight members who shall be appointed as follows: Two by the Governor, one of whom shall be nationally recognized as an active investigator in the field of stem cell research and one of whom shall have background and experience in the field of bioethics; one each by the president pro tempore of the Senate and the speaker of the House of Representative, who shall have background and experience in private sector stem cell research and development; one each by the majority leaders of the Senate and House of Representatives, who shall be academic researchers specializing in stem cell research; one by the minority leader of the Senate, who shall have background and experience in either private or public sector stem cell research and development or related research fields, including, but not limited to, embryology, genetics or cellular biology; and one by the minority leader of the House of Representatives, who shall have background and experience in business or financial investments. Members shall serve for a term of four
years commencing on October first, except that members first appointed by the Governor and the majority leaders of the Senate and House of Representatives shall serve for a term of two years. No member may serve for more than two consecutive four-year terms and no member may serve concurrently on the Stem Cell Research Peer Review Committee established pursuant to section 4 of this act. All initial appointments to the committee shall be made by October 1, 2005. Any vacancy shall be filled by the appointing authority.

(b) The Commissioner of Public Health shall serve as the chairperson of the committee and shall schedule the first meeting of the committee, which shall be held no later than December 1, 2005.

(c) All members appointed to the committee shall work to advance embryonic and human adult stem cell research. Any member who fails to attend three consecutive meetings or who fails to attend fifty per cent of all meetings held during any calendar year shall be deemed to have resigned from the committee.

(d) All members shall be deemed public officials and shall adhere to the code of ethics for public officials set forth in chapter 10 of the general statutes. No member shall participate in the affairs of the committee with respect to the review or consideration of any grant-in-aid application filed by such member or by any eligible institution in which such member has a financial interest, or with whom such member engages in any business, employment, transaction or professional activity.

(e) The Stem Cell Research Advisory Committee shall (1) develop, in consultation with the Commissioner of Public Health, a donated funds program to encourage the development of funds other than state appropriations for embryonic and human adult stem cell research in this state, (2) examine and identify specific ways to improve and promote for-profit and not-for-profit embryonic and human adult stem cell and related research in the state, including, but not limited to, identifying both public and private funding sources for such research, maintaining existing embryonic and human adult stem cell related businesses, recruiting new embryonic and human adult stem cell related businesses to the state and recruiting scientists and researchers in such field to the state, (3) establish and administer, in consultation with the Commissioner of Public Health, a stem cell research grant program which shall provide grants-in-aid to eligible institutions for the advancement of embryonic or human adult stem cell research in this state pursuant to section 2 of this act, and (4) monitor the stem cell research conducted by eligible institutions that receive such grants-in-aid.

(f) Connecticut Innovations, Incorporated shall serve as administrative staff of the committee and shall assist the committee in (1) developing the application for the grants-in-aid authorized under subsection (e) of this section, (2) reviewing such applications, (3) preparing and executing any assistance agreements or other agreements in connection with the awarding of such grants-in-aid, and (4) performing such other administrative duties as the committee deems necessary.

(g) Not later than June 30, 2007, and annually thereafter until June 30, 2015, the Stem Cell Research Advisory Committee shall report, in accordance with section 11-4a of the general statutes, to the Governor and the General Assembly on (1) the amount of grants-in-aid awarded to eligible institutions from the Stem Cell Research Fund pursuant to section 2 of this act, (2) the recipients of such grants-in-aid, and (3) the current status of stem cell research in the state.
Sec. 4. (NEW) (Effective from passage) (a) There is established a Stem Cell Research Peer Review Committee. The committee shall consist of five members appointed by the Commissioner of Public Health. All members appointed to the committee shall (1) have demonstrated knowledge and understanding of the ethical and medical implications of embryonic and human adult stem cell research or related research fields, including, but not limited to, embryology, genetics or cellular biology, (2) have practical research experience in human adult or embryonic stem cell research or related research fields, including, but not limited to, embryology, genetics or cellular biology, and (3) work to advance embryonic and human adult stem cell research. Members shall serve for a term of four years commencing on October first, except that three members first appointed by the Commissioner of Public Health shall serve for a term of two years. No member may serve for more than two consecutive four-year terms and no member may serve concurrently on the Stem Cell Research Advisory Committee established pursuant to section 3 of this act. All initial appointments to the committee shall be made by October 1, 2005. Any member who fails to attend three consecutive meetings or who fails to attend fifty per cent of all meetings held during any calendar year shall be deemed to have resigned from the committee.

(b) All members shall be deemed public officials and shall adhere to the code of ethics for public officials set forth in chapter 10 of the general statutes. No member shall participate in the affairs of the committee with respect to the review or consideration of any grant-in-aid application filed by such member or by any eligible institution with whom such member has a financial interest in, or engages in any business, employment, transaction or professional activity.

(c) Prior to the awarding of any grants-in-aid for embryonic or human adult stem cell research pursuant to section 2 of this act, the Stem Cell Research Peer Review Committee shall review all applications submitted by eligible institutions for such grants-in-aid and make recommendations to the Commissioner of Public Health and the Stem Cell Research Advisory Committee established pursuant to section 3 of this act with respect to the ethical and scientific merit of each application.

(d) The Peer Review Committee shall establish guidelines for the rating and scoring of such applications by the Stem Cell Research Peer Review Committee.

(e) All members of the committee shall become and remain fully cognizant of the National Academies Guidelines For Human Embryonic Stem Cell Research, as from time to time amended, and the committee may make recommendations to the Stem Cell Research Advisory Committee and the Commissioner of Public Health concerning the adoption of said guidelines, in whole or in part, in the form of regulations adopted pursuant to chapter 54 of the general statutes.

Sec. 5. Subsection (c) of section 4-28e of the general statutes is repealed and the following is substituted in lieu thereof (Effective from passage):

(c) (1) For the fiscal year ending June 30, 2001, disbursements from the Tobacco Settlement Fund shall be made as follows: (A) To the General Fund in the amount identified as “Transfer from Tobacco Settlement Fund” in the General Fund revenue schedule adopted by the General Assembly; (B) to the Department of Mental Health and Addiction Services for a grant to the regional action councils in the amount of five hundred thousand dollars; and (C) to the Tobacco and Health Trust Fund in an amount equal to nineteen million five hundred thousand dollars.
(2) For the fiscal year ending June 30, 2002, and each fiscal year thereafter, disbursements from the Tobacco Settlement Fund shall be made as follows: (A) To the Tobacco and Health Trust Fund in an amount equal to twelve million dollars; (B) to the Biomedical Research Trust Fund in an amount equal to four million dollars; (C) to the General Fund in the amount identified as "Transfer from Tobacco Settlement Fund" in the General Fund revenue schedule adopted by the General Assembly; and (D) any remainder to the Tobacco and Health Trust Fund.

(3) For each of the fiscal years ending June 30, 2008, to June 30, 2015, inclusive, the sum of ten million dollars shall be disbursed from the Tobacco Settlement Fund to the Stem Cell Research Fund established by section 2 of this act, for grants-in-aid to eligible institutions for the purpose of conducting embryonic or human adult stem cell research.

Sec. 6. (Effective from passage) The sum of twenty million dollars is appropriated to the Stem Cell Research Fund established by section 2 of this act, from the General Fund, for the fiscal year ending June 30, 2005.

Approved June 15, 2005
APPENDIX B
Committee Membership Lists
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## Stem Cell Research Peer Review Committee

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