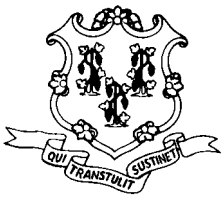
Keeping Connecticut Healthy

REPORT TO GOVERNOR RELL
AND
THE GENERAL ASSEMBLY

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

JUNE 30, 2008

Connecticut Stem Cell Research Advisory Committee
J. Robert Galvin, M.D., M.P.H., M.B.A., Commissioner; Chair



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Report to Governor Rell 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 appropriated the sum of twenty million dollars to the newly established Stem Cell Research Fund for the purpose of grants-in-aid for conducting embryonic or human adult stem cell research. For each of the fiscal years ending June 30, 2008 to June 30, 2015, inclusive, the Act specified that an additional ten million dollars should be disbursed from the State's Tobacco Settlement Fund to the Stem Cell Research Fund to support additional grants-in-aid.

The Act was subsequently codified at Section 19a-32 of the Connecticut General Statutes. In accordance with Section 19a-32f(g), the Stem Cell Research Advisory Committee shall 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. This report covers the period from July 1, 2007 through June 30, 2008. Significant accomplishments during this time period include:

- Establishment of the University of Connecticut Stem Cell Core Facility
- Establishment of the Yale Stem Cell Center
- Development and issuance of a Request for Proposals in August 2007
- Receipt of 87 applications for grants-in-aid on November 1, 2007
- Review, rating and ranking of 87 grants-in-aid applications on scientific and ethical merit by the Stem Cell Research Peer Review Committee
- Review and rating of 87 grants-in-aid applications on March 31 and April 1, 2008 by the Stem Cell Research Advisory Committee
- Successful awarding of 22 grants-in-aid totaling $9.84 million to researchers based in Farmington, New Haven, and Storrs
- Successful branding of Connecticut as an International Center of Excellence for Stem Cell Research

Since passage of the enabling legislation in 2005, the State of Connecticut has allocated a total of $29.62 million in support of stem cell researchers.

I. INTRODUCTION AND BACKGROUND

Public Act 05-149, "An Act Permitting Stem Cell Research and Banning the Cloning of Human Beings"[1] (the Act), was approved by the General Assembly of the State of Connecticut and signed into law by Governor M. Jodi Rell on June 15, 2005. The Act appropriated the sum of twenty million dollars to the newly established Stem Cell Research Fund for the purpose of grants-in-aid for conducting embryonic or human adult stem cell research. In addition, for each of the fiscal years ending June 30, 2008 to June 30, 2015, inclusive, the Act specified that an additional ten million dollars should be disbursed from the State's Tobacco Settlement Fund to the Stem Cell Research Fund to support additional grants-in-aid.

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[2] 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. In accordance with Section 3(g)(3) of the Act, the Stem Cell Research Advisory Committee is required 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 this act, (2) the recipients of such grants-in-aid, and (3) the current status of stem cell research in the State.

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, 2007 to June 30, 2008 was the development of the Request for Proposals, receipt and review of the 87 applications for grant-in-aid, and the allocation of available dollars.

From November 2007 through February 2008, the 14 member Peer Review Committee completed the enormous task of rating and ranking each of the 87 applications for grants-in-aid from Connecticut's research community. During a teleconferenced meeting on March 5, 2008, 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 17, September 18, and October 16, 2007, and on January 15, February 19, March 18, March 31, April 1, April 15, May 20 and June 17, 2008. The SCR Advisory Committee completed their review of applications and allocation of grants-in-aid during the two-day meeting on March 31 and April 1, 2008. All meetings are open to the public with notices and agendas on both the DPH and Secretary of State's websites. Minutes and transcripts of all 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 22 grants-in-aid totaling $9.84 million to researchers in Farmington, Storrs and New Haven, including the first award to a private company, Evergen Biotechnologies.

Maintaining and Enhancing the Human Embryonic Stem Cell Core at the Yale Stem Cell Center, **Yale University Stem Cell Center**, **New Haven**, Haifan Lin, PhD, Principal Investigator, **$1,800,000.**

Translational Studies in Monkeys of hESCs for Treatment of Parkinson's Disease, **Yale University School of Medicine**, **New Haven**, D. Eugene Redmond, Jr., MD, Principal Investigator, **$1,120,000.**

Establishing the Connecticut Therapeutic Cloning Core Facility – From Startup Technology/Feasibility Tests to SCNT/ntESC Derivation Services, **Evergen Biotechnologies, Inc., Storrs**, Jang-Won Lee, PhD, Principal Investigator, **$900,000.**

Production and Validation of Patient-Matched Pluipotent Cells for Improved Cutaneous Repair, **University of Connecticut Center of Regenerative Biology**, **Storrs**, Theodore Rasmussen, PhD., Principal Investigator, **$634,880**.

Tyrosone Phosphorylation Profiles Associated with Self-Renewal and Differentiation of hESC, **University of Connecticut Health Center, Farmington**, Bruce Mayer, PhD., Principal Investigator, **$450,000**.

*Directed Differentiation of ESCs into Cochlear Precursors for Transplantation as Treatment of Deafnes*s, **University of Connecticut Health Center, Farmington,** D. Kent Morest, MD, Principal Investigator, **$450,000**.

Modeling Motor Neuron Degeneration in Spinal Muscular Atrophy Using hESCs, **University of Connecticut Health Center, Farmington**, Xuejun Li, PhD., Principal Investigator, **$450,000**.

Human Embryonic and Adult Stem Cell for Vascular Regeneration, **Yale University School of Medicine, New Haven**, Laura E. Niklason, MD, PhD, Principal Investigator, **$450,000**.

Effect of Hypoxia on Neural Stem Cells and the Function in CAN Repair, **Yale University, New Haven**, Flora M. Vaccarino, MD, Principal Investigator, **$449,771.40**

Wnt Signaling and Cardiomyocyte Differentiation from hESCs, **Yale University, New Haven**, Dianqing Wu, PhD, Principal Investigator, **$446,818.50**.

Flow Cytometry Core for the Study of hESC, **University of Connecticut Health Center, Farmington**, Hector Leonardo Aguila, PhD., Principal Investigator, **$250,000**.

Cortical neuronal protection in spinal cord injury following transplantation of dissociated neurospheres derived from human embryonic stem cells, **Yale University School of Medicine, New Haven**, Masanori Sasaki, MD, PhD, Principal Investigator, **$200,000**.

Molecular Control of Pluripotency in Human Embryonic Stem Cell, **Yale Stem Cell Center, New Haven**, Natalia Ivanova, PhD, Principal Investigator, **$200,000**.

Cytokine-induced Production of Transplantable Hematopoietic Stem Cells from Human ES Cells, **University of Connecticut Health Center, Farmington**, Laijun Lai, MD, Principal Investigator, **$200,000**.

Functional Use of Embryonic Stem Cells for Kidney Repair, **Yale University, New Haven**, Lloyd G. Cantley, MD, Principal Investigator, **$200,000**.

VRK-1-mediated Regulation of p53 in the Human ES Cell Cycle, **Yale University, New Haven**, Valerie Reinke, PhD, Principal Investigator, **$200,000**.

Definitive Hematopoitic Differentiation of hESCs under Feeder-Free and Serum-Free Conditions, **Yale University**, Caihong Qiu, PhD, Principal Investigator, **$200,000**.

Differentiation of hESC Lines to Neural Crest Derived Trabecular Meshwork Like Cells – Implications in Glaucoma, **University of Connecticut Health Center, Farmington**, Dharamainder Choudhary, PhD., Principal Investigator, **$200,000**.

Targeting Lineage Committed Stem Cells to Damaged Intestinal Mucosa, **University of Connecticut Health Center, Farmington**, Daniel W. Rosenberg, PhD., Principal Investigator, **$450,000**.

The Role of the piRNA Pathway in Epigenetic Regulation of hESCs, **Yale University, New Haven**, Qiaoqiao Wang, PhD., Principal Investigator, **$200,000**.

Early Differentiation Markers in hESCs: Identification and Characterization of Candidates, **University of Connecticut Center for Regenerative Biology, Storrs**, Mark G. Carter, PhD., Principal Investigator, **$200,000**.

Regulation hESC-dervied Neural Stem Cells by Notch Signaling, **Yale University, New Haven**, Joshua Breunig, PhD, Principal Investigator, **$188,676.**

IV. INTERNATIONAL CENTER OF EXCELLENCE FOR STEM CELL RESEARCH

Connecticut continues to be recognized within the international stem cell research community, both at a research and policy making level. The Connecticut DPH also continues its close relationship with the United Kingdom, Canada, and the International Society of Stem Cell Research (ISSCR).

At the invitation of the British Consulate offices in Boston, three Connecticut representatives joined a delegation of American scientists and policy makers during a four day trip to the United Kingdom from October 14 – 18, 2007. Connecticut attendees were Commissioner McDonald from the Department of Economic and Community Development, Paul Pescatello, President and CEO of CURE, and Marc Lalande, Professor and Chair of UConn's Department of Genetics and Developmental Biology. The purpose of the trip was to explore transatlantic partnerships.

The Interstate Alliance on Stem Cell Research (IASCR) met twice during the period covered by this report, including a meeting hosted by the British Consulate office in Boston in October 2008. In addition to the nine original states, participants in the IASCR now include both the British and Canadian Consulates, the ISSCR, the Minnesota and Harvard Stem Cell Institutes, the Coalition for the Advancement of Medical Research and the Juvenile Diabetes Research Foundation. Connecticut continues to serve as the chair of the IASCR, and additional information on the IASCR can be found at http://www.iascr.org/

Plans are well underway with respect to Connecticut's next international research symposium, StemCONN 09, Connecticut's International Stem Cell Research Symposium. The event will bring the worldwide stem cell research community to New Haven on March 23–24, 2009. StemCONN 09 will build on the success of StemCONN 07, and will cover the most recent discoveries surrounding stem cell research and associated policy, ethical and commercial challenges. StemCONN 09 will provide Connecticut's three stem cell research academic institutions an opportunity to showcase their successful programs, noted below. Additional information is available at http://stemconn.org/

V. CONNECTICUT'S STEM CELL RESEARCH COMMUNITY

Since passage of the enabling legislation in 2005, the State of Connecticut has allocated a total of $29.62 million in support of stem cell researchers at the University of Connecticut, Yale University, and Wesleyan University. During state fiscal year 2008, the SCR Advisory Committee prioritized awards to the private research sector, and allocated the first award to a private company, Evergen Biotechnologies.

The following describes the state of publicly funded stem cell research efforts at Yale University, Wesleyan University, and the University of Connecticut.

Yale University[3]

The funding from the State of Connecticut has triggered an expansion of stem cell research at Yale University and presented new opportunities to collaborate with colleagues at the University of Connecticut Health Center, and the University of Connecticut at Storrs, Wesleyan University, and a number of biotech industries throughout the State.

Specifically, this funding has assisted in building an infrastructure of core facilities, initiating new research projects, recruiting new faculty, and stimulating new collaborations both within the Yale community and throughout Connecticut.

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 has established the following core laboratories, funded by a Core Facility grant from the Connecticut Stem Cell Research Fund. This Core grant allowed Yale to purchase major equipment and supplies, as well as salaries for the experts who manage the Cores.

a. The Human Embryonic Stem Cell (hESC) Core. This Core serves as a storage, distribution, and training center for hESCs, and is developing new hESC lines and 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 is fully operational. It has trained 10 investigators from seven labs, and is supplying hESC cell lines to nine labs.

b. The 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 AOBS 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 provids service to 18 investigators from 10 labs.

c. Fluorescence Analysis and Cell Sorting (FACS) Core. The Yale School of Medicine purchased a BD FACSAria 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 a similar Core on the Medical School campus and between the two Cores they are providing service to 776 investigators.

d. Genomics Core. This Core consists of a Cellomics High Throughput Cell Screen system and an Illumina Genome Analyzer. The Cellomics Cell Screen system was provided by the Yale School of Medicine and installed on the second floor of the Amistad building for analysis of stem cells including non-federally approved hESC lines.

[3] The progress report on Connecticut supported stem cell research was prepared by Haifin Lin, Ph.D., Director, Diane Krause, M.D., Ph.D., Associate Director, and Paula Wilson, M.B.A., Administrator

The Illumina Genome Analyzer, purchased in part by a Hybrid Grant from the SCR Fund and support from Yale, has been temporarily installed in the KBT building at Yale, where there is staff with the expertise to set up and train on the operation of the system. This analyzer has succeeded in trial runs and will be in service soon. 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. In addition, it will allow the Connecticut Stem Cell Initiative to dovetail with the Connecticut Genomics Initiative.

e. Communications System. A videoconferencing system was purchased and installed to facilitate sharing of information on hESC research with colleagues throughout Connecticut and around the world.

2. **New Research Projects**

Dr. Diane Krause, Professor of Laboratory Medicine and Associate Professor of YSCC: Acute megakaryoblastic leukemia (AMKL) is a type of leukemia that occurs almost exclusively in newborns and infants less than 2 months of age. The disease has a very poor prognosis with a median survival of only 8 months. Dr. Krause's laboratory is studying the function of the gene called MKL that is mutated in the cancer cells of some patients with AMKL. The Krause laboratory has demonstrated that levels of this protein change during the maturation of normal blood cells, and they are testing hypotheses regarding how MKL affects cells to make them leukemic. Since this leukemia occurs in newborn infants, it is likely that the cancer stem cell for this leukemia arises prior to birth during fetal development. Studies in the Krause laboratory over the past year have begun to clarify the mechanism by which MKL affects blood growth during fetal development in mice, and, most relevant to the CT stem cell initiative, they have used human embryonic stem cells as a model of human prenatal development to study the role of MKL in blood maturation in people. This grant is highly relevant to the CT stem cell initiative because the grant funding provided has led directly to the expansion of their leukemia research program to studies on the role of MKL in blood development from hESCs.

Dr. Erik M. Shapiro, Assistant Professor of Diagnostic Radiology: This research uses magnetic resonance imaging (MRI) methodologies to monitor the migration of adult neural precursor cells in the brain. Furthermore, Dr. Shapiro's lab is developing approaches to steer these immature neurons to specific sites in the brain, where they could potentially be beneficial for a variety of diseases, including stroke, Parkinson's disease or ALS. The core technological principal of the research is the incorporation of iron oxide particles into neural stem cells. When the stem cells divide to make young neurons, particles can be transferred to these cells. As they move through the brain, MRI can detect these cells at single cell resolution. The initial characterization of this baseline migration is currently being carried out in the Molecular and Cellular MRI Laboratory, in close collaboration with the YSCC and Magnetic Resonance Research Center. This involves a linear combination of MRI, image processing, tissue pathology and statistical analysis. As early experiments resulted in variable cell labelling, a rigorous study evaluating label titration in the brain is concurrently being carried out. This titration, the first of its kind, will greatly enhance our ability to longitudinally monitor cell migration in the brain by reducing background and increasing cellular specificity.

Dr. Michael Snyder, Professor of Molecular, Cellular and Developmental Biology: Dr. Snyder's lab has begun to profile protein and RNA that is expressed in hESCs. This will generate a list of components that are expressed in these cells and potentially describe new components and pathways involved in hESC self renewal and differentiation. Their studies will also help us understand how hESCs are regulated during cell differentiation into neural cells. This information is ultimately expected to be valuable for controlling hESC differentiation for therapeutic purposes.

Dr. Haifan Lin, Professor of Cell Biology and Director, YSCC: The Lin lab studies the translational control of the human embryonic stem cell fate. The differences between hESCs and their daughter neural cells are controlled by a set of genes that are active either in the stem cells or in the neural cells. However, often these genes are equally active at the transcriptional level, producing equal amounts of their corresponding messenger RNAs. What causes the ultimate difference in the gene activity is whether these messenger RNAs guide the production of their corresponding proteins. Dr. Lin's lab has shown in model organisms that this level of regulation is essential in controlling the ability of stem cells to maintain their own identity and to produce specialized cells, such as neural cells. Yet to their knowledge, no one has been studying this important mechanism. Their progress has allowed them for the first time to systematically embark on this study. If their aims are achieved, they will be able to demonstrate the function of a few "master' proteins, such as Pum1, Pum2, HILI, and HIWI, in controlling this process. These proteins then will be effective therapeutic molecules or targets for us to harness the directed differentiation of hESCs to a desired type of neural cells for eventual medical applications.

Dr. Sherman Weissman, Professor of Genetics: Dr. Weissman's lab is developing procedures for identifying those genes that are needed for forming specific types of cells in the human nervous system. To do this, they are using human stem cells to derive various types of nervous system cells in culture. They will then use methods for decreasing the level of expression of each gene individually to find which genes are needed for forming different cell types in the nervous system and also which genes limit the formation of each cell type. Currently they are developing the best procedures for infecting the human ES cells and neural precursors with viruses that express small RNAs able to suppress the expression of single genes, and novel technologies for simply detecting which of these small RNAs affect the patterns of neural differentiation.

Dr. Weimin Zhong, Associate Professor of Molecular, Cellular and Developmental Biology: During the extended period of organogenesis and tissue maintenance during development, there is an essential need for proper balance between self-renewal and differentiation, since a failure in either task can lead to malformation and malfunction of tissues and organs. Asymmetric cell division is a process by which a cell divides to produce two different daughter cells. Conceptually, stem cells can simultaneously self-renew and differentiate by dividing asymmetrically to produce one daughter cell that remains as a stem cell and another that differentiates. Stem cells, however, may also need to divide symmetrically to produce two stem cells, which can quickly expand their population when responding to tissue injuries, or to generate two differentiated cells, when large numbers of stem cells are no longer necessary towards the end of organogenesis and tissue repair. In other words, understanding the division

patterns of stem cells – particularly how they are regulated under normal and pathological conditions – may facilitate a key goal of stem-cell research, which is to repair or replace damaged tissues by introducing exogenous stem cells or expanding endogenous populations. Dr. Zhong's lab research attempts to probe the mechanisms that regulate the behavior of stem cells by changing their patterns of division, as a means to find ways to expand stem cells when tissue repair becomes necessary or to eliminate stem cells in cancers, which are believed to be diseases of stem cells.

Dr. Eleni Markakis, Assistant Professor of Psychiatry: Dr. Markakis' work seeks to simplify the culture of hESCs so that more laboratories may work with them to develop treatments for diseases of the central nervous system. Specifically, Dr. Markakis' work, if achieved, should allow human embryonic stem cell researchers to produce more reliable and repeatable results on stem cell differentiation, allowing standardization for pharmaceutical and clinical applications.

Dr. Yingqun Huang, Assistant Professor of Obstetrics/Gynecology: The ultimate goal of Dr. Huang's research is to understand the molecular mechanism of fragile X syndrome (FXS) in order to aid in the development of effective therapeutic interventions. FXS is caused by a mutation in the *FMR1* gene that leads to the loss of expression of its encoded protein FMRP. FMRP is an RNA-binding protein that functions through interaction with mRNAs. Her lab is working to identify mRNA targets regulated by FMRP in neuronal progenitor cells derived from hESCs. This would enable them to gain novel molecular insights into how this disease may develop in the very early stage of human brains. To facilitate target identification, they are creating and characterizing *FMR1* gene-knockout (*FMR1*-KO) hESC lines to be used to derive negative control materials for their next set of experiments, in which they will validate the function of FMR1 targets. To date, they have successfully made the targeting construct to be used to permanently silence the *FMR1*gene in the hESCs.

3. **Recruitment of Leading Stem Cell Researchers**

The funding from the State has positioned the YSCC as a leader in stem cell research. This has aided in the recruitment of Drs. Natalia Ivanova and Caihong Qiu. Dr. Invanova is an assistant professor of Genetics and the first Robert McCluskey Yale Scholar in 2007. Dr. Ivanova is a young scientist who has already made landmark contributions to stem cell research. She came to Yale from Princeton University, where she was a research scholar in the Department of Molecular Biology. Her research focuses on embryonic stem cells and their contributions to early mouse development. Dr. Caihong Qiu came from the Human Embryonic Stem Cell Core at the Albert Einstein Medical College.

A new faculty search is underway to recruit two additional faculty members in 2008. Yale received 64 applications from stem cell experts from around the world, including 13 applications from California and 16 from Massachusetts. Other applications came from major stem cell research states such as Maryland, New York, and New Jersey. The Search Committee selected seven candidates with exceptional credentials to interview for the positions. The individuals have been received with overwhelming enthusiasm by the current faculty at Yale. Of the seven, four candidates will return to Yale for a second visit and to begin negotiations for their

recruitment packages. Because of the support from the State, Yale is in a position to compete with major stem cell research centers in the world for these candidates.

In addition, with the current funding from the State, YSCC has recruited four non-faculty stem cell researchers:

a. Qiaoqiao Wang, a senior postdoctoral associate who received her Ph.D. from UConn and then obtained postdoctoral training at UConn and Yale, has been recruited to work on Pum-mediated translational regulation of hESC differentiation down the neuronal lineage.
b. Jonathan Saxe, a postdoctoral associate, received his Ph.D. in Molecular and Medical Pharmacology from the University of California, Los Angeles, where his graduate work focused on the identification and characterization of small molecule probes for manipulating neural stem cell differentiation.
c. Sadie Smith, a postdoctoral associate, received her Ph.D. in Animal Science from the University of Connecticut under Xiangzhong Yang.
d. Elana Miriami, a postdoctoral associate, received her Ph.D. in Genetics from the Hebrew University of Jerusalem, Israel, and her graduate work focused on bioinformatics.

4. Internal and External Collaborations

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 will receive funding from the 2008 SCR Fund will use hESC lines from the hESC Core Facility and rely on the expertise of Dr. Qiu, who was recruited to the YSCC last year 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 CURE has flourished as they work together to organize biannual retreats and StemCONN meetings. The last two retreats in November and March were extremely successful in that they provided a forum for stem cell researchers with varied levels of experience to learn from each other. The retreat at Yale on November 27, 2007 included presentations from Dr. Mickie Bhatia from the Stem Cell and Cancer Research Institute in Canada and Dr. Linzhao Cheng from the Stem Cell Program at Johns Hopkins Institute for Cell Engineering, and attracted more than 100 attendees from all over the State. Other talks were provided by junior faculty from UConn, Wesleyan, and Yale and the day ended with a discussion forum with updates from the directors of the two hESC Cores in the State, creating great synergy among the stem cell researchers in the State of Connecticut.

Additional collaborations with 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 create many opportunities for Yale to help establish a stem cell industry in the State.

The University of Connecticut[4]

In the first year of funding provided by the Connecticut SCR Fund, researchers at the University of Connecticut (UConn) made significant progress towards the development of a world-class human embryonic stem cell (hESC) research program. In particular, the funding allowed some of our best scientists to integrate human embryonic stem cells into their research programs. On September 26 2007, the University established a Stem Cell Institute as a cross-campus collaborative effort to enhance the research environment for the University's stem cell investigators. The University of Connecticut Stem Cell Institute, under the leadership of **Dr. Marc Lalande,** will also foster and facilitate interactions with our partners at Yale and Wesleyan Universities.

The establishment of the hESC core facility was key to allowing our researchers to initiate the exciting hESC research projects supported by the Connecticut Stem Cell Research Fund.

1. The Human Embryonic Stem Cell Core Facility

A major accomplishment was the launching of the human embryonic stem cell (hESC) core facility at the University of Connecticut Health Center. This core facility was successful in designing, establishing and providing training sessions for members of the research teams from across the State of Connecticut. The UConn hESC core facility, directed by **Dr. Ren-He Xu**, is fully prepared to meet the ever-increasing demand by Connecticut scientists for human embryonic stem cells and stem cell-related training and services, and help advance stem cell-based therapies to treating human diseases.

Training: In this first year, hESC core facility banked nine human embryonic stem cell lines, and provided cells to more than 30 laboratories at University of Connecticut, Wesleyan University, and Yale University. The facility held 11 training sessions and trained more than 70 researchers statewide on stem cell culture techniques. The core lab also provided quality control and technical support to stem cell researchers. Moreover, the hESC core obtained approvals by the Internal Review Board and Embryonic Stem Cell Research Oversight and receive extra embryos donated to in vitro fertilization clinics. The hESC core is now ready to derive new human embryonic stem cell lines from the donated embryos. The sub-cores for cell sorting and gene delivery have also started to provide services to stem cell researchers. To meet the stem cell education mission, stem cell seminars were teleconferenced to UConn Storrs, Wesleyan, and Yale, and three outreach seminars were organized at other colleges in the state. University of Connecticut researchers also participated in the regional retreats held at Yale in November 2007 and at Wesleyan in March 2008.

Infrastructure and Equipment: The University of Connecticut has invested over $1 million to establish and equip the human embryonic stem cell (hESC) core facility. In order to further advance our cutting edge stem cell research, the University has recently acquired two major pieces of equipment: $500,000 for the purchase of state-of-the-art FACS equipment for sorting and purifying stem cells and $725,000 for the acquisition of a high throughput SOLEXA DNA

[4] The progress report on Connecticut supported stem cell research was provided by Marc Lalande, Ph.D., Director, University of Connecticut Stem Cell Institute

sequencer to study in detail the genes and chromosomes of embryonic stem cells.

2. Research Programs

The group project grant headed by **Dr. David Rowe** aims to direct progenitor cells derived from hESC into musculoskeletal lineages. This program, distributed between Storrs and Farmington, routinely uses videoconferencing as a primary method of communication. Many of the investigators use fluorescent protein markers as well as gene expression microarrays to follow and characterize the different musculoskeletal lineages. The first year of this grant was designed to establish the basic framework for evaluating the potential of human embryonic stem (hES) cell derived bone progenitors to repair a bone defect. A murine model for testing bone repair was established using murine stem cells carrying a fluorescent visual marker to identify the host and donor contribution to the bone repair. A colony of immuno-compromised mice capable of sustaining a human transplant was established and the process to place the visual reporters into these mice was initiated.

For the microarray gene expression profiling of the different lineages, **Dr. Dong-Guk Shin** and the others in the musculoskeletal program have selected the low density array (LDA) platform and have developed a website that enables the scientists to enter their preferences of genes to be included in LDA. **Dr. Leonardo Aguila** is identifying stages of development responsible for the generation of bone, cartilage and muscle with the goal of sequentially dissecting defined stages along the progression of these tissues for generation of specific antibodies to isolate cells that could be used in the repair of these tissues after injury or degeneration.

UConn scientists are also working to develop culture systems and conditions that enable hESCs to uniformly differentiate into the chondrogenic lineage. hESCs are a potentially powerful tool for the repair of cartilage through the development of procedures for directing the differentiation of hESCs into cartilage cells (chondrocytes) or chondrogenic progenitor cells. **Dr. Robert Kosher** and his colleagues have successfully developed culture systems and conditions that promote quite uniform differentiation of hESCs into the chondrocyte lineage. Furthermore, they have made the unprecedented observation that undifferentiated hESCs have the ability to directly differentiate into the chondrocyte lineage when provided with the appropriate cellular environment and signaling molecules. Under these conditions the hESCs show more uniform cartilage differentiation than has previously been reported. This result is important for eventually using a homogenous population of hESC-derived chondrogenic cells for repair of damaged or diseased cartilage.

Dr. Lisa Kuhn has seeded aggregates of hESCs onto three surfaces: collagen, hydroxyapatite and tissue culture plastic and subjected them to mineralization medium. Under these specialized conditions, the morphology of the hESCs appeared more uniform on the hydroxyapatite and collagen surfaces than the tissue culture plastic. They are awaiting analysis of the gene expression to identify the proportion of cells that have become bone or cartilage cells. **Dr. Mei Wei** is subjecting freeze-drying scaffolds, that are seeded with osteoprogenitor cells, to in vitro cell culture conditions. She and her colleagues are in the process of optimizing the fabrication parameters of this group of scaffolds for improved cell attachment, proliferation and differentiation.

Dr. Alex Lichtler and his colleagues have created a viral vector with green fluorescent marker protein that contains the promoter for a gene called brachyury, which is expressed in mesoderm cells. They have developed efficient and reliable methods for putting this viral vector into hESC, and are currently growing hESC containing the vector. **Dr. David Goldhamer** and his group have derived transgenic mice with a conditional allele of the muscle-specific transcription factor MyoD, and also plan to test the ability of hESC-derived mesodermal stem/progenitor cells to repair muscle damage. The development of effective cell-based therapies for skeletal tissues in the craniofacial complex is dependent on isolation and identification of stem/progenitor cells capable of regenerating skeletal tissues with structural, morphological and mechanical properties similar to craniofacial skeleton *in situ*. To address these issues, **Dr. Mina Mina** is optimizing conditions for generation and identification of neural crest progenitors from human embryonic stem cells and plans to examine the formation of bone and teeth from these cells. **Dr. Stephen Clark** is also a member of the Rowe group grant who has identified conditions for improved wound healing, specifically the application of exogenous cells to a wound site.

Dr. Gordon Carmichael examined in detail the expression in hESCs of proteins involved in double strand RNA (dsRNA) response pathways. Interestingly, one of these pathways, the interferon response pathway, appears to be missing in these cells. This is not only scientifically interesting, but also has practical implications relating to how dsRNAs can be utilized for gene silencing in stem cells. A second dsRNA response pathway, RNA editing, is robust in hESCs.
Dr. Joseph LoTurco plans to direct the patterns of migration of neurons derived from hESCs into damaged or diseased brain. Towards this end, his laboratory has established the culture of the H9 hESC line and differentiated these into neuronal progenitor cells. They have also constructed DNA vectors that can now be used to alter the hESC-derived neurons in order to allow the manipulation of their migration in tissues.

Alternative splicing is one of the most important mechanisms by which gene expression is regulated and as many as 75% of human genes use this process of gene regulation. **Dr. Brenton Graveley** is working to identify the alternative splicing events that occur in undifferentiated hESCs and in hESCs undergoing differentiation into different cell types as well as the roles of specific RNA binding proteins such as Musashi1, in controlling these alternative splicing events. His laboratory developed a custom microarray that contained 385,000 probes to all of the splice junctions in the human genome to identify changes in alternative splicing that occur upon the addition of BMP4 to hESCs. The preliminary analysis suggests that there are several genes containing exons that are alternatively spliced upon the addition of BMP4. These results suggest that the process of alternative splicing does indeed have an important role in hESC cell differentiation.

Dr. Ren-He Xu's laboratory has identified two essential signaling pathways governing the early fates of human embryonic stem cells. The BMP pathway promotes the cells to differentiate, whereas the TGFb pathway sustains their self-renewal. He is searching for target genes for both pathways in hESCs by using a global searching strategy that involves chromatin-immunoprecipitation (ChIP) and promoter arrays. He has identified ChIP-grade antibodies for SMADs, made constructs to express SMADs or their inhibitors, and searched some potential target genes of the TGFb and iBMP pathways. He has also formulated specialized medium (TeSR) to culture hESCs in defined conditions to facilitate the analysis of the signaling pathways. **Dr. Akiko Nishiyama** proposes to use a polymer containing glial cells derived from

hESCs in order to optimize axonal regeneration. After completing training in the hESC core facility, members of her laboratory have successfully begun to grow hESCs. They are now exploring techniques to grow the cells to a high density for storage and are optimizing procedures for differentiating hESCs into neural cells.

Dr. Tai-Hsi Fan who is developing a microfluidic hESC cultivation system for the quantitative analysis of molecular transport and population kinetics; **Dr. Theodore Rasmussen** who is developing assays to determine the epigenetic status of hESCs using novel assays for histone modifications; **Dr. Winfried Krueger** who is studying the relationship between cell cycle and stem and somatic cell re-progamming efficiency; **Dr. Mark Carter** is generating insulin producing cells from hESCs; **Dr. Bei Liu** who studies the potential of ES cells to deliver de-differentiation antigens to the immune system to generate anti-tumor immunity; **Dr. James Li** who is developing an efficient and reproducible method, while circumventing many drawbacks of conventional approaches, for genetic modifications of hESCs; **Dr. Craig Nelson** is developing a single cell gene expression assay in order to perform lineage mapping of early hESC differentiation.

3. Research Recruitments

One goal of the State's stem cell initiative is to attract internationally renowned stem cell experts. The University of Connecticut is fortunate to have recruited **Dr. Xuejun Li** who is a leading authority on the differentiation of human embryonic stem cells into neurons and, more specifically, motor neurons. Dr. Li came to Connecticut from the WiCell research institute, the laboratory in Wisconsin where human embryonic stem cells were first produced. Dr. Li, an Assistant Professor of Neuroscience, is using hESCs to study Spinal Muscular Atrophy, a disease of neuronal degeneration.

Dr. Stephen Crocker, who was lured to Connecticut from the Scripps Research Institute in California, is examining the response of the nervous system to myelin injury and immune system attack, as this relates to diseases like Multiple Sclerosis. Dr. Crocker, an Assistant Professor of Neuroscience, plans to use hESCs to study brain regeneration and recovery. The University of Connecticut plans to recruit many more stem cell experts into a 117,000 sq ft building at 400 Farmington Ave that will be fully renovated within the next two years. The fully refurbished and state-of-the-art building will house the Stem Cell Institute and the hESC core facility.

4. External Collaborations

We have hosted stem cell experts from around the world in our stem cell seminar series. In addition to strengthening our interactions with Yale and Wesleyan, new collaborations are being formed with scientists from institutions that include Dartmouth College, Harvard Medical School, University of Wisconsin-Madison, UCLA and the Scripps Institute. We also plan to forge links with researchers outside the United States in order to further advance our mission.

5. Summary

The researchers of the University of Connecticut Stem Cell Institute are extremely grateful to the citizens and legislators of the State of Connecticut for their generous support of these important and exciting projects. For the coming year, University of Connecticut scientists are dedicated to making discoveries that will speed the development of stem cell therapies.

Wesleyan University

1. 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.

2. Research Projects

Dr. Grabel reports that they have made significant progress in their first year at the Grabel Laboratory. They have documented three significant scientific developments: 1) Hedgehog signaling acts in a novel autocrine fashion to promote the survival of ESC-derived neural stem cells (Cai et al, 2008). 2) Region-specific cues direct the fate of ESC-derived neural stem cell s transplanted to the hippocampus in a mouse seizure model of epilepsy (Carpentino et al, 2007); and 3) SDF-1 promotes the migration of ESC-derived neural stem cells.

In addition, they have published a review on ESC neurogenesis (Cai and Grabel, 2007) and have also co-written an introduction and edited a volume of Metaphilosophy on Stem Cell Ethics which has been turned into a book, "Stem Cell Research: the Ethical Issues" by Blackwell.

3. External Collaborations

Janice Naegele: The ongoing collaboration with the Naegele laboratory continues to be an integral and essential component of our projects. New contributions include the use of EEG recordings to measure seizure activity.

Gloster Aaron: This interaction has produced the first patch clamp recordings from transplant-derived cells within the granule cell layer of the dentate gyrus and suggest functional integration into the host circuitry. These studies are key to determining the ability of ESC-derived neurons to function in a host brain.

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 cell survival and experiments using FACS isolated Sox1-GFP+ NSCs led to our identification of these cells as the source of Sonic hedgehog and to our hypothesis that Hh acts in an autocrine fashion to promote NSC survival. FACS isolation of Sox1-GFP+ cells is also key to our ongoing investigation of the how to remove teratocarcinoma-forming potential from the cell population prior to transplant.

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

VI. SUMMARY

Passage of the Public Act 05-149 positioned Connecticut as just the third state in the nation, behind only California and New Jersey, in providing public funding in support of embryonic and human adult stem cell research. Since passage of the enabling legislation in 2005, the State of Connecticut has allocated a total of $29.62 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, and supported new research efforts from established and junior faculty members at the University of Connecticut, Yale University, and Wesleyan University.

Connecticut has successfully positioned itself as a leader in both the national and international stem cell research communities. With robust academic stem cell research programs, with vehicles such as StemCONN and the Interstate Alliance for Stem Cell Research, and with strong collaborative relationships with the International Society for Stem Cell Research, the United Kingdom and Canada, Connecticut will maintain its status as an International Center of Excellence for stem cell research.

APPENDIX A
Public Act 05-149

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

Stem Cell Research Advisory Committee

Member	Affiliation
Robert Galvin, M.D., M.P.H., M.B.A. **Chair**	Commissioner CT Department of Public Health 410 Capitol Avenue P.O. Box 340308 Hartford, CT 06134-0308
Treena Livingston Arinzeh, Ph.D.	Associate Professor Department of Biomedical Engineering New Jersey Institute of Technology University Heights 614 Fenster Hall Newark, NJ 07102-1982
Ernesto Canalis, M.D.	St. Francis Hospital and Medical Center Department of Research 114 Woodland Street Hartford, CT 06105-1299
Gerald Fishbone, M.D.	Hospital of St. Raphael New Haven, CT
Myron Genel, M.D.	Professor Emeritus of Pediatrics Child Health Research Center Yale University School of Medicine Department of Pediatrics 333 Cedar Street P.O. Box 208081 New Haven, CT 06520-8081
Paul L. Huang, M.D., Ph.D.	Director, Cardiac Metabolic Syndrome Program Associate Director, Cardiovascular Research Center Associate Professor of Medicine, Harvard Medical School Massachusetts General Hospital East 149 Thirteenth Street Charlestown, MA 02129
Charles G. Jennings, Ph.D. **Resigned 4/15/08**	McGovern Institute for Brain Research MIT Building 46, Room 3160 77 Massachusetts Avenue Cambridge, MA 02139
Ann Kiessling, Ph.D.	Harvard Institutes of Medicine 4 Blackfan Circle, Room 248 Boston, MA 02115
Julius Landwirth, M.D., J.D.	Associate Director, Yale Interdisciplinary Center for Bioethics and Donaghue Initiative in Biomedical and Behavioral Research Ethics

	Yale Interdisciplinary Center for Bioethics 87 Trumbull Street New Haven, CT 06520-8209
Stephen Latham, Ph.D., J.D.	Quinnipiac University School of Law 275 Mt. Carmel Avenue Hamden, CT 06518
Robert Mandelkern	Parkinson Disease Representative to CT Stem Cell Coalition
Paul Pescatello, Ph.D., J.D.	President & CEO CT United for Research Excellence, Inc. 300 George Street, Suite 561 New Haven, CT 06511
Amy Wagers, Ph.D.	Joslin Diabetes Center Dev and Stem Cell Biology Room 620 C One Joslin Place Boston, MA 02215
Milton B. Wallack, DDS	295 Washington Avenue Hamden, CT 06518

Stem Cell Research Peer Review Committee

Member	Affiliation
Linzhao Cheng, Ph.D.	Associate Investigator and Co-Director Stem Cell Program, Institute for Cell Engineering Johns Hopkins School of Medicine Broadway Research Building, Room 747 733 North Broadway Baltimore, MD 21205
Dieter C. Gruenert, Ph.D.	Senior Scientist California Pacific Medical Center Research Institute Adjunct Professor, Department of Laboratory Medicine University of California, San Francisco Adjunct Professor, Department of Medicine University of Vermont 475 Brannan Street, Suite 220 San Francisco, California 94107
D. Leanne Jones, Ph.D.	Assistant Professor Department of Biology Salk Institute for Biological Studies P.O. Box 85800 San Diego, California 92186-5800
Michael Kyba, Ph.D.	Assistant Professor Center for Developmental Biology The University of Texas Southwestern Medical Center at Dallas 6000 Harry Hines Boulevard, NB5.208 Dallas, Texas 75390-9133
Majlinda Lako, Ph.D	Senior Lecturer Institute of Human Genetics University of Newcastle upon Tyne International Centre for Life Central Parkway Newcastle upon Tyne, NE1 3BZ United Kingdom
M. William Lensch, Ph.D.	Instructor in Pediatrics, Harvard Medical School Senior Scientist, George Q. Daley Laboratory Division of Hematology/Oncology Children's Hospital Boston 300 Longwood Avenue Boston, Massachusetts 02115
Linheng Li, Ph.D.	Associate Investigator Stowers Institute for Medical Research 1000 East 50th Street Kansas City, Missouri 64110

Hanna Mikkola, M.D., Ph.D.	Assistant Professor Department of Molecular, Cell and Developmental Biology Institute for Stem Cell Biology and Medicine University of California, Los Angeles 621 Charles E. Young Drive South, 2204 Los Angeles, California 90092
Martin Pera, Ph.D.	Institute for Stem Cell and Regenerative Medicine University of Southern California 1501 San Pablo Street, ZNI-535 Los Angeles, California 90033-2821
Gary S. Stein, Ph.D.	The Gerald L. Haidak, M.D. and Zelda S. Haidak Distinguished Professor and Chair of Cell Biology Professor of Medicine Deputy Director, University of Massachusetts Memorial Cancer Center Department of Cell Biology University of Massachusetts Medical School 55 Lake Avenue, North Worcester, MA 01655
Miodrag Stojkovic, Ph.D.	Deputy Director Principe Felipe Centro de Investigacion C/ E.P. Avda. Autopista del Saler 16-3 (Junto Oceanografico) 46013 Valencia, Spain
Catherine M. Verfaillie, M.D.	Director, Stamcel Instituute Leuven Katholieke Universiteit Leuven Onderwijs & Navorsing 1 Herestraat 49, bus 804 3000 Leuven Belgium
Leslie Weiner, M.D.	Chair, Department of Neurology Keck School of Medicine of USC 2025 Zonal Ave., RMR 506 Los Angeles, California 90033
Ian Wilmut, Ph.D.	Professor Reproductive Science Centre for Reproductive Biology Reproductive and Developmental Sciences The Queen's Medical Research Institute The University of Edinburgh 47 Little France Crescent Edinburgh EH16 4TJ, Scotland

APPENDIX C
Stem Cell Research Application and Guidelines

Connecticut Stem Cell Research Grants Program

Submission Deadline – November 1, 2007

Proposal Instructions

It is the intent of the Connecticut Stem Cell Research Advisory Committee to fund the best stem cell research proposals that Connecticut scientists can offer. The Advisory Committee intends to maintain a program of outstanding science that will continue Connecticut's pioneering role as a center of international excellence and leadership in stem cell research.

Purpose

The Connecticut Stem Cell Research Grants Program, authorized in the Connecticut General Statutes (C.G.S.) Sections 19a-32d through 19a-32g, a Statute Permitting Stem Cell Research and Banning the Cloning of Human Beings, supports the advancement of embryonic and/or human adult stem cell research in Connecticut.

Proposals must describe the applicant's organization, the applicant's plans for stem cell research, proposed funding for such research from sources other than the state of Connecticut, and 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 grants.

The Connecticut Stem Cell Research Advisory Committee, in consultation with the Commissioner of Public Health, administers and monitors the grant program. Connecticut Innovations, Inc. serves as administrative staff of the Advisory Committee, reviewing applications, and preparing and executing assistance agreements for the grants.

Ten million dollars is available in the Connecticut Stem Cell Research Grants Fund through June 30, 2008. For each of the fiscal years ending June 30, 2009 to June 30, 2015, inclusive, ten million dollars will also be available.

Definitions

Embryonic Stem Cells: 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.

Nuclear Transfer: the replacement of the nucleus of a human egg with a nucleus from another human cell.

Eligible Applicant: a nonprofit, tax-exempt academic institution of higher education, a hospital that conducts biomedical research, or any entity that conducts biomedical research or embryonic or human adult stem cell research. The institution, hospital, or company must have its primary location in Connecticut.

Institutional Review Committee: the local Institutional Review Committee (IRB) specified in 21 USC 360j(g)(3)(A)(i), and when applicable, an institutional review board established in accordance with the requirements of 45CFR 46, Subpart A.

ESCRO Committee: an Embryonic Stem Cell Research Oversight (ESCRO) committee which operates in accordance with the National Academy of Sciences' Guidelines for Human Embryonic Stem Cell Research as amended from time to time.

Overview

It is the intent of the Connecticut Stem Cell Research Grants Program to consider funding any form of stem cell research, but priority will be given to human embryonic stem cell research that is not currently eligible for federal funding. Other types of stem cell research will also be eligible, with priority given to studies with clear potential relevance to human health. Animal models are not excluded from consideration but applicants will need to demonstrate a direct relevance to human stem cell biology and its therapeutic implications.

Who May Submit

Connecticut researchers engaged in the advancement of embryonic or human adult stem cell research are encouraged to submit proposals. Research must be conducted at an eligible academic institution, hospital or company. Researchers at such entities may apply for any category of grants. The researcher's institution, hospital, or company must undertake responsibility for financial administration of the grant and for overall compliance with rules governing research at that entity. Except as specified, applicants at academic research institutions must be faculty members. Non-tenure track faculty members may apply if their institutional policies permit them to hold independent grants. Postdoctoral fellows may apply for seed grants with the support of a faculty sponsor. Applicants from hospitals or companies must be permitted by their organization to hold research grants.

When to Submit

Submit a one page letter of intent by September 15, 2007.

Completed hard copy, signed proposals, as well as electronic copies of proposals are due at Connecticut Innovations by 4:30 p.m. on November 1, 2007.

Where to Submit

(1) Letters of intent should be sent electronically to stemcellinfo@ctinnovations.com

(2) An original signed proposal should be delivered to:

Connecticut Stem Cell Research Grants Program
Connecticut Innovations
c/o Nancy Rion
200 Corporate Place, 3rd Floor
Rocky Hill, CT 06067

(3) An electronic copy of the proposal in PDF format should be sent to stemcellinfo@ctinnovations.com

Refer questions to Nancy Rion: 860-563-5851 or stemcellinfo@ctinnovations.com

Special Considerations for Human Embryonic Stem Cell (hESC) Research

A priority for the Connecticut Stem Cell Research Grants Program is to support research on hESC that are not currently eligible for federal funding. The state is committed to the highest standard of ethical oversight and transparency, and expects all grant recipients to be in full compliance with all applicable laws, regulations and guidelines, including a review and approval by the Institutional Review Board (IRB) and Embryonic Stem Cell Research Oversight (ESCRO) Committee, when applicable, regarding this type of research.

The grantee's institution, hospital or company must establish an ESCRO committee, or establish an affiliation with an existing ESCRO committee, along the lines recommended by the National Academies Guidelines for Human Embryonic Stem Cell Research, as amended from time to time, http://www.nap.edu/books/0309096537/html to oversee all hESC research at the institution, hospital or company. Each grantee's institution, hospital or company must submit a list of members of the ESCRO committee along with a copy of the policies and procedures of the ESCRO committee prior to the release of funds. The Advisory Committee reserves the right to delay or decline funding if it is not satisfied that the ESCRO committee is appropriately established and constituted.

If an applicant institution, hospital or company does not have an established ESCRO committee, the application must summarize the entity's plans and timetable for establishing or affiliating with an ESCRO committee. Release of funds is contingent on submission of a list of members of the ESCRO committee along with a copy of the policies and procedures of the ESCRO committee as well as ESCRO approval of the project.

If research on non-federal hESC lines is to be conducted in a research environment that also receives federal funding support, the institution, hospital or company must have established a detailed policy for the segregation of funding in compliance with federal funding restrictions. The policy must be in place before the release of funds.

Types of awards

Applications will be considered for (1) Seed Grants, (2) Established Investigators, (3) Group Projects, and (4) Core Facilities. For this funding cycle, total annual funding for Seed Grant Awards will be at least 10% of the total annual budget for the Connecticut Stem Cell Research Grants Program.

1. Seed Grant Awards: These awards are intended to support the early stages of projects that are not yet ready for larger scale funding whether from federal or nonfederal sources. Junior researchers in hospitals and companies are particularly encouraged to apply. In academic institutions, priority will be given to junior faculty members at the start of their independent careers. Established investigators new to stem cell research may apply for seed grants. Postdoctoral fellows, or equivalent, may apply with the support of a faculty sponsor or equivalent. A letter from the sponsor indicating support of the proposal must be included with the application and must describe the applicant's level of independence, as well as other resources/funding available for the project.

Requested funding for a Seed Grant Award may be up to $200,000 (including indirect costs) and may be expended over 2 years. The yearly budget must not exceed $100,000. Project Descriptions for Seed Grant applications are limited to 5 pages (inclusive of the main text, methodology, figures and legends). Other proposal requirements are described under "Guidelines for Preparation of Proposals."

2. Established Investigator Awards: These awards are intended for investigators with a track record of independent research including prior grant support and regular peer reviewed publications.

Requested funding for an Established Investigator Award may be up to $500,000 (including indirect costs) and may be expended over 4 years. Funding is encouraged to be evenly budgeted over the duration of the award. Project Descriptions for Established Investigator applications are limited to 10 pages (inclusive of the main text, methodology, figures, and legends). Other proposal requirements are described under "Guidelines for Preparation of Proposals."

3. Group Project Awards: These awards are intended to support coordinated approaches to ambitious strategic goals that are beyond the scope of a typical single laboratory. Priority will be given to projects involving collaboration across disciplines and/or institutions, and proposals should include explanations of the need for collaboration, along with plans for managing the collaborative process, including division of responsibilities among collaborators and timelines for achieving expected project milestones. If more than one institution, hospital or company is involved, the proposed budget must specify how funding is to be distributed between collaborating entities. As with other grants, eligibility for funding is restricted to researchers at CT institutions, hospitals or companies. Group Projects may have multiple co-principal investigators, but one individual must be identified as the lead investigator and primary contact with the Connecticut Stem Cell Research Program.

Requested funding for a Group Project Award may be up to $2 million (including indirect costs) and may be budgeted for up to 4 years. Descriptions for Group Project applications are limited to 50 pages (inclusive of the main text, methodology, figures, and legends). Other proposal requirements are described under "Guidelines for Preparation of Proposals."

4. Core Facilities Awards: These awards are intended to provide shared core facilities for stem cell researchers at eligible Connecticut institutions, hospitals or companies.

Applications will be considered for additional support of already established cores and for new cores that are beyond the means of most individual labs, that will be made widely accessible to the CT stem cell research community, and that are likely to advance stem cell research throughout the state. Proposals must include an explanation of the need for a new core or expansion of an existing core, along with estimates of likely capacity and usage. Previously funded cores should provide specific details in their budget justification about the necessity of additional funding, including explanation of how new and existing funding will be integrated without overlap.

Applicants should demonstrate a proven expertise in the relevant technology and ability to provide a high quality service. Funds may be used to cover equipment, salaries or other costs associated with establishing and operating cores. Cores will also be allowed to establish a reasonable fee-for-service schedule in order to recover additional costs associated with their operation. Proposed fees must be specified and approved by the institution, hospital or company.

Requested funding for a Core Facilities Award may be up to $2.5 million (including indirect costs) and may be budgeted for up to 4 years. Project Descriptions for Core Facilities applications are limited to 50 pages (inclusive of the main text, methodology, figures, and legends). Other proposal requirements are described under "Guidelines for Preparation of Proposals."

Note: Group Project Awards may include shared equipment as part of their budget. Core Facility Awards are distinct, however, in that they are intended specifically to provide services to the wider Connecticut

research community, rather than being restricted to participants in a specific collaborative project or to members of the host institution, hospital or company.

Note: Group Project Awards and Core Facilities Awards may under special cases include startup funds for investigators yet to be hired. Such proposals require detailed justification, including the identification of the person to be hired *and* a detailed description of his/her contribution to the specific project. Release of funds will be contingent on the investigator accepting and taking up the position. Justification must include the need for additional recruitment and an explanation of how the funding will be used to support the overall goals of the project. Funds may not be used for general research infrastructure not directly related to the goals of the Connecticut Stem Cell Research Grants Program.

Selection Criteria

The criteria to be employed in the evaluation shall include, but not be limited to, the following:

A. Scientific merit of the proposed research
B. Conformance to high ethical standards
C. Ability to perform the proposed research
D. Commitment of host institution, hospital or company and (where applicable) collaborators to the proposed project, including cost sharing
E. Potential for collaboration across disciplines and institutions, hospitals or companies
F. Benefits (including financial benefits) to the state of Connecticut
G. Alignment with funding priorities as determined by the Connecticut Stem Cell Research Advisory Committee

I. Proposal Review

The Connecticut Stem Cell Research Peer Review Committee will review all proposals and make recommendations to the Connecticut Stem Cell Research Advisory Committee with respect to the ethical and scientific merit of each proposal. The Peer Review Committee and the Stem Cell Research Advisory Committee will be guided by the National Academies Guidelines for Human Embryonic Stem Cell Research, as amended from time to time, http://www.nap.edu/books/0309096537/html and C.G.S. Sections 19a-32d through 19a-32g.

The Advisory Committee, in consultation with the Commissioner of Public Health, will make the funding decisions. The Advisory Committee reserves the right and discretion to fund one or more components or defined parts of an application's proposed research project. In the event of such a determination, the applicant will be required to submit a revised budget reflecting the Advisory Committee's funding decision and such other information as the Advisory committee may require.

Decisions regarding funding are anticipated on or after April 2008.

II. Funding

Notification of funding approval will be made by the Commissioner of Public Health.

The institution, hospital or company will then sign a contract indicating that the institution, hospital or company is in compliance with the requirements of applicable Connecticut General Statutes, Executive Orders and other administrative requirements. The institution, hospital or company must establish an ESCRO committee or become affiliated with an ESCRO committee that will review and approve proposals involving the use or creation of human embryonic stem cells and must submit a list of members of the ESCRO committee along with a copy of the policies and procedures of the committee prior to the release of funds. The Advisory Committee reserves the right to delay or decline funding if it is not satisfied that the ESCRO committee is appropriately established and constituted.

The funding period begins on the effective date specified in the contract. Expenditures incurred before the effective date of the contract may not be charged against the project. Expenditures may be made within 60 days after the scheduled expiration date of the contract, only to honor services or goods encumbered before the expiration date. Any requests for rollovers or extensions must be approved by the Advisory Committee.

Transmittal of Funds

Funds will be transmitted to the institution, hospital or company over the duration of the grant according to each year's budget request. Multi-year projects will receive the first installment immediately following the signing of the contract for the project, and subsequent installments will be transmitted after technical and fiscal progress reports are received and approved.

Audit of Funds

Expenditures by institutions, hospitals or companies may be subject to audit. Entities submitting proposals for funding must agree to cooperate by providing information for audit and a full review of the project.

III. Guidelines for Preparation of Letter of Intent and Proposals

Letter of Intent

Applicants are asked to submit a letter of intent that includes the following information:

- Title of proposed project
- Type of award
- Estimate of requested funding amount
- Contact information for Principal Investigator
- Brief description of proposed project

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows staff to estimate the potential review workload and plan the review.

Proposal

Original signed proposals must be stapled in the upper left-hand corner but otherwise unbound with pages numbered at the bottom, with one-inch margins, and with 12 point font. They may be single-spaced and shall be printed only on one side. Any reprints, appendices, or other materials to be considered with the proposal must be attached to the original proposal as well as electronic copies. The electronic copy of the proposal and all attachments should be sent in one (1) PDF file.

The total length of the proposal is dependent upon the type of award being sought and is outlined above under the heading "Types of Awards." Proposals that do not follow the prescribed format or are incomplete when they are submitted may be rejected as ineligible for consideration.

Proposals shall include the following:

1. Cover Page (Attachment I)

Use the format provided in Attachment I. A proposal is incomplete if any of this information or signatures is omitted. The Cover Page must be signed by the Vice President for Research or authorized official to confirm institutional approval for the application including financial as well as other types of regulatory compliance (see #9 Special Considerations).

A separate page (Attachment I), should be completed by an investigator at each participating institution, hospital or company. For projects with multiple investigators, the lead investigator should be indicated.

2. Project Summary (Attachment II)

Use the format provided in Attachment II. The summary shall include a statement of objectives and the scientific methods to be employed written in lay language. Limit summaries to the space provided on Attachment II. Note: Because the Project Summary will be available to the public, do not include proprietary information in the Summary.

3. Table of Contents

4. Project Description

Page limits for each type of Award are defined above under the heading "Types of Awards." The description of the project shall include the following subsections:

a. Project Objectives and Significance of Proposed Work

Describe the goals and objectives of the project. Discuss the rationale for choosing these objectives. Explain how these objectives compare to the state of the art and what distinguishes this proposed work from other efforts.

b. Project Plan

Describe the technical plan over the life of the project, how the proposed work will be organized into tasks and how the tasks are interrelated. Define clear, quantitative milestones and provide an expected schedule for reaching these milestones, including regulatory approvals where applicable. For projects involving several co-investigators and/or institutions, hospitals or companies, describe the expected contributions of each participant. Summarize the technical tasks that must be accomplished, with special emphasis on new or innovative technologies required for success of the project. Describe the technical challenges and the approach to overcoming any barriers. Assess the probability of success of this project.

c. Intellectual Property

Describe the plans and timeline to protect the intellectual property. Describe the plans and timeline for licensing the technology. As required by C.G.S. Sections 19a-32d through 19a-32g, applicants must submit *"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 grants-in-aid."*

In evaluating proposed arrangements, it is expected that, at a minimum, the State of Connecticut shall be entitled to royalties, at a rate of 5%, on gross revenues generated from the exploitation of any invention or intellectual property that is conceived, created or developed during the stem cell research and development activities, and during the term of the funding or at any time during the 12-month

period immediately following the term of funding, and which was made possible (in whole or in part) by, or otherwise resulted (in whole or in part) from, the funding.

For purposes of this section, an "invention" shall be defined as any product, process, apparatus, technique, creation, development or other discovery, and "intellectual property" shall be defined as any invention and any instructions, processes, formulas, methods and information, including, without limitation, biological, chemical, pharmacological, toxicological, pharmaceutical, physical and analytical, clinical, safety, manufacturing and quality control data and information (i.e. "know-how"). All inventions shall be promptly reported to the Department of Public Health and Connecticut Innovations.

d. Bibliography

List the existing research and technology base that supports the proposed work.

5. Evidence of Commitment

a. Commitment of Institution, Hospital or Company and other Collaborators

Describe the commitment of the institution, hospital or company and that of other collaborators to this project.

b. Commitment of the Key People

- Describe their qualifications
- Describe the focus of each person's efforts
- Estimate the percentage of effort each person will devote to this project
- Describe the project management plan

c. Commitment to Sharing Resources

The Connecticut Stem Cell Research Grants Program expects grant recipients and their institutions, hospitals or companies to share reagents, data and protocols developed in connection with these grants. In particular such resources shall be made freely available to other Connecticut-based researchers. Describe plans for sharing such anticipated resources. If this is expected to involve significant costs to the recipient institution, hospital or company, the budget may include a component to cover these costs.

d. Financial Commitment from other Sources

Describe financial commitments to the project from other sources. As required by C.G.S. Section 19a-32e, applicants must submit "proposed funding for such research from sources other than the state of Connecticut."

e. Available Facilities and Major Items of Equipment

Describe the facilities and major equipment available for this project.

6. Biographical Sketches

Submit a brief biographical sketch, including patents, selected publications, and recently funded projects for each principal investigator (four page maximum per person). For Seed Grant Awards, provide a biographical sketch for the applicant and, if appropriate, for the faculty sponsor.

7. Budget

a. Budget Detail (Attachment III)

Each proposal must contain a budget for each year of support requested and a cumulative budget for

the full term of requested support. Identify each year's request ("First year," "Second year," or "Cumulative Budget") at the top right of each page. Use the prescribed budget format provided in Attachment III.

Salaries and Wages: List the names of the principal investigator(s) and other senior associates and the estimated amount of time dedicated to this project (number of academic-year, summer, or calendar-year person-months if proposal is from academic institution) for which funding is requested. Salaries requested must be consistent with the regular practices of the institution, hospital or company.

Hospitals and companies may not use Connecticut Stem Cell Research Grant Funds to augment the existing salaries of investigators. For proposals from academic institutions, Connecticut Stem Cell Research Grant Funds may not be used to augment the total salary or rate of salary of faculty members during the period covered by the term of faculty appointment. Nor may funds be used to reimburse faculty members for consulting or other time in addition to a regular full-time institutional salary covering the same general period of employment. For postdocs, graduate students and technical staff, etc., list only the total number of persons and total amount of salaries per year in each category.

Fringe Benefits: If the usual accounting practices of the institution, hospital or company provide that its contributions to employee benefits (social security, retirement, etc.) be treated as direct costs, funds may be requested to defray such expenses as a direct cost.

Equipment: The Connecticut Stem Cell Research Grants Program wishes to avoid expensive duplication of research infrastructure wherever possible. Therefore, any budget requests for major equipment must be carefully justified.

Identify items exceeding $1,000 or more and a useful life of more than one year as Permanent Equipment. Special purpose research equipment having a unit acquisition cost of $10,000 or more purchased or leased with project funding is subject to reasonable research equipment inventory controls, maintenance procedures, and organizational policies that enhance its multiple or shared use on other projects, if the other use does not interfere with the work on the project for which the equipment is acquired.

Travel: Funds may be requested for fieldwork necessary to carrying out the project and up to $5,000 per year per principal investigator to travel to conferences to present findings. (Documentation of expenses will be required in subsequent fiscal reports).

Other Direct Costs: The budget should itemize other anticipated direct costs, including materials and supplies, publication costs, and computer services. Other examples include payments to service charges, and construction of equipment or systems not available off-the-shelf.

Publication Costs/Page Charges: The budget may request funds for the costs of publishing the results of the project, including costs of reports, reprints, page charges, other journal costs and necessary illustrations.

Cost of sharing reagents: If the project is expected to generate reagents or data that will be of

general value to the research community, the budget may include a component to cover the reasonable costs of generating and distributing such resources.

Indirect Costs: Budgets may include indirect costs, which may not exceed 25 percent of the Modified Total Direct Costs (MTDC). MTDC are described in Attachment A of OMB Circular A122 and consist of all salaries and wages, fringe benefits, materials and supplies, services, travel, and sub-grants and subcontracts up to the first $25,000 of each sub-grant or subcontract (regardless of the period covered by the sub-grant or subcontract). Equipment, capital expenditures, charges for patient care, rental costs and the portion in excess of $25,000 shall be excluded from MTDC. Participant support costs shall generally be excluded from MTDC.

b. Budget Explanation/Justification

In a separate section titled "Budget Explanation/ Justification," clearly delineate the specific use and justification of funds. Breakdowns should be as accurate and specific as possible. For equipment funding requests, describe and justify each piece of requested equipment. Identify location of use. If comparable equipment is available at the institution, hospital or company, explain why it cannot be used.

Include in this section a detailed description of the contributions from the institution, hospital or company and collaborators.

8. Special Considerations

Several situations require written assurance that appropriate institutional, hospital or company clearance procedures are in place:

1. Projects that involve the use of recombinant DNA and/or hazardous reagents.
2. Projects that involve use of human eggs, embryos and/or human embryonic stem cells.
3. Projects that involve the use of human subjects.
4. Projects that involve the use of animal subjects.

All proposals must be in compliance with federal, state and local laws and all applicable permitting requirements. Prior to conducting research involving human embryonic stem cells, documentation verifying that any human embryos, embryonic stem cells, unfertilized human eggs or human sperm used in such research have been donated voluntarily as required by C.G.S. Sections 19a-32d through 19a-32g must be provided to the Commissioner of Public Health on a form available from the Connecticut Department of Public Health, www.dph.state.ct.us/stemcell at Verification Form.

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9. Appendix

Letters of commitment from the institution, hospital or company and collaborators should be included. For applicants at the postdoctoral fellow stage, a letter of support from the faculty sponsor should also be included.

V. Project Administration

Responsibility for general supervision of all project activities rests with the institution, hospital or company.

Adherence to Original Budget Estimates

Reallocation of more than 10 percent of the annual budget requires the approval of Connecticut Innovations. The written request to re-budget, signed by the principal investigator and the authorized institution, hospital or company representative, must fully explain the need for re-budgeting. Reallocation of more than 20% of the annual budget also requires approval of the Advisory Committee.

Changes in Personnel

Timely notification to Connecticut Innovations (who will notify the Advisory Committee and Peer Review Committee) is required for any change in any principal investigators before or after signing the contract. All changes involving senior personnel must be approved by the Advisory Committee. If the principal investigator terminates employment with the institution, hospital or company, the entity may terminate the project, or when appropriate, propose to the Advisory Committee a substitute principal investigator to continue the project.

Funding cannot be transferred from the institution, hospital or company except when the grantee moves to another eligible entity within Connecticut and the transfer receives the prior approval of the Advisory Committee.

Equipment

Title to equipment purchased or fabricated with funds or matching funds vests in the institution, hospital or company.

Project Reports

Principal investigators are required to submit **Annual Technical Progress Reports.** Reports shall

- summarize activity during the past year,
- describe progress with reference to scheduled milestones,
- identify any significant scientific developments and all invention disclosures,
- describe collaborative work,
- describe any problems encountered,
- include a statement of expenditures for the past 12 months
- include a two page summary in lay language suitable for the public and press.

Institutions, hospitals and companies are required to submit **Semi-Annual Fiscal Reports** for each project.

Failure to submit required reports could result in deferral of subsequent installment payments or termination of support and forfeiture of funds.

The Advisory Committee and the Peer Review Committee and/or their designees reserve the right to conduct site visits for funded projects.

Principal investigators are required to submit a **Final Report** within 90 days after the expiration of a contract**.** This report must include information needed for purposes of program management, evaluation, fiscal accountability, and informing the public about the results of research supported under the Connecticut Stem Cell Research Grants Program.

Acknowledgment of Support and Disclaimer

Any publication, oral presentation, or meeting abstract based on research activity supported by the funding must contain the following acknowledgment: "This material is based upon work supported by the State of Connecticut under the Connecticut Stem Cell Research Grants Program. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the State of Connecticut."

Proposal as Public Record

Funded proposals will become a matter of public record and will be available to the public, except as described below. Information or material that Connecticut Innovations and the institution, hospital or

company mutually agree to be of a privileged nature will be held in confidence to the extent permitted by law. Without assuming any liability for inadvertent disclosure, Connecticut Innovations will seek to limit dissemination of such information only to its employees, selected employees at the Connecticut Department of Public Health, the Connecticut Stem Cell Peer Review Committee, and to the Connecticut Stem Cell Research Advisory Committee. Accordingly, a proposal which indicates the inclusion of "Proprietary and Privileged Information" on the cover page, will be released to the Connecticut Stem Cell Peer Review Committee, and to the Connecticut Stem Cell Research Advisory Committee only after those reviewers have signed a non-disclosure document reflecting applicable state law. Applicants are required to identify the words or paragraphs on specific pages of the application that contain trade secrets or other proprietary information. Notwithstanding the foregoing, all applicable laws governing access to public records will be observed.

Inventions, Software, and Copyrights

As required by C.G.S. Sections 19a-32d through 19a-32g, applicants must submit *"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 grants-in-aid."* The State of Connecticut encourages the publication and distribution of the results of the project performed under its funding. The Commissioner of Public Health retains the right to use published materials resulting from the performance of work under Connecticut Stem Cell Research Grants Program funding for state purposes.

Attachment I CT Stem Cell Research Proposal

Cover Page

Attachment I should be completed by the principal investigator of each participating institution. For projects with multiple investigators, the lead investigator should be indicated.

Indicate type of project:

_____ Seed Grant

_____ Established Investigator Grant

_____ Group Project Grant

_____ Core Facility Grant

Title of Project

Institution/Hospital/Company

PI Name(and sponsor name where applicable) **Signature (s)**

I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibilities for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

PI Department/Business Address

PI Phone **PI Email**

Amount Requested $

Authorized Representative **Title**

I certify that the statements herein are true, complete and accurate to the best of knowledge, and accept the obligation to comply with all terms and conditions of the Connecticut Stem Cell Research Grants Program ***and all applicable laws and ethical standards*** if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

Signature **Date**

Items included in Project (check where appropriate)

☐ Proprietary and Privileged Information (identify such words or paragraphs on specific pages)

☐ Recombinant DNA and/or Hazardous Reagents
☐ Human Eggs, Embryos and/or Human Embryonic Stem Cells
☐ Animal Subjects
☐ Human Subjects

Attachment II CT Stem Cell Research Proposal

Project Summary (in Non-Scientific Language)

Attachment II should be completed by the principal investigator of each participating institution, hospital of company. For projects with multiple investigators, the lead investigator should be indicated.

Title of Project

Amount requested $

Principal Investigator

Institution/Hospital/Company

Collaborator (s)

One sentence description. This Project's purpose is to

Project Summary (Limit to this side of form)

Attachment III CT Stem Cell Research Proposal Budget

To be completed by each Institution/Hospital/Company

Budget for Year ___
Cumulative Budget ___

A. Senior Personnel PI, CO-PI's, Faculty and Other Senior Associates (List each separately with Title and Organization on Budget Explanation page. Show number in brackets.)	**Grant Funded Person-Mos.**	**Funding Requests**
1.		
2.		
3.		
4. ( ) Others (List individually on Budget Explanation Page)		
5. ( ) Total Senior Personnel (1-4)		
B. Other Personnel (Show numbers in brackets)		
1. ( ) Post-Doctoral Associates		
2. ( ) Other Professionals (Technician, Programmer, Etc.)		
3. ( ) Graduate Students		
4. ( ) Other -Specify		
Total Salaries And Wages (A&B)		
C. Fringe Benefits (If charged as Direct Costs)		
Total Salaries, Wages, and Fringe Benefits (A+B+C)		
D. Permanent Equipment (Describe on Budget Explanation Page)		
E. Other Direct Costs (Describe details on Budget Explanation Page)		
1. Materials And Supplies		
2. Publication Costs/Page Charges		
3. Computer Services		
4. Other		
Total Other Direct Costs		
F. Indirect Costs (Describe on Budget Explanation Page)		
G. Total Costs (A Through F)		
H. Projected Revenues		
I. Total Contributions from Other Sources		

APPENDIX D
Listing of Published Articles

Publication List

Published

Gruen, L., Grabel, L., and Singer, P. (2007) Guest editors of special issue of Metaphilosophy 38 “Stem Cell Research: the Ethical Issues”. Blackwell. Also published by Blackwell as a book, *Stem Cell Research, the Ethical Issues*.

Carpentino, J., Hartman, N., Grabel, L., and Naegele, J. (2008) Region-specific differentiation of ES-derived neural progenitor transplants into the adult mouse hippocampus following seizures. Journal of Neuroscience Research 86: 512-524.

Cai, C., and Grabel, L. (2007) Directing the differentiation of embryonic stem cells to neural stem cells. Developmental Dynamics, 236(12):3255-66.

Gruen, L., and Grabel, L. (2006) Scientific and ethical roadblocks to human embryonic stem cell therapy. Stem Cells 24: 2162-2176.

Gruen, L and Grabel, L. (2007) Ethics and Stem Cell Research, Introductory Paper. Metaphilosophy 38:137-152. Also published by Blackwell as a book, *Stem Cell Research, the Ethical Issues*.

In Press

Cai, C., Thorne, J., and Grabel, L. (2008) Hedgehog serves as a mitogen and survival factor during embryonic stem cell neurogenesis. Stem Cells.

Submitted for Publication

L-L Chen, J. DeCerbo and Gordon G. Carmichael: “Alu-element mediated gene silencing” (2008), submitted to *EMBO Journal*.

J. Zhou, Q. Wang and Gordon G. Carmichael: “On the mechanism of heterochromation formation by the RNA-binding protein vigilin” (2008), submitted to *RNA*.

In Preparation

Zhong, W., Waern, K., Nagalakshmi, U., and M. Snyder 2008. Methods for Scoring transcribed regions and boundaries using RNA Sequencing.