# A Strategy for Advancing Stem Cell Research and Regenerative Medicine at the University of Massachusetts

## *Report to the Board of Trustees Committee on Science, Technology & Research*

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**University of Massachusetts Stem Cell R&D Working Group**


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## CASE STATEMENT SUMMARY

Stem cell research and regenerative medicine holds enormous promise for cures of debilitating diseases – such as cancer, juvenile diabetes, Alzheimer's, and Parkinson's – and improved medical care for the millions of Americans suffering from them. Academic and industry researchers across the world are currently working to unlock their potential, but the absence of leadership by the U.S. government has slowed progress. In response, many states are investing significant resources to advance research, develop new therapies and in the process, capture downstream economic benefits. The Commonwealth, however, has not yet chosen to act.

Massachusetts, while an undisputed leader in the life sciences, cannot afford to remain idle. Through a strategic investment in the University of Massachusetts (UMass), the Commonwealth can provide infrastructure and resources to develop new cures and better treat disease, continue to move its public research university along its path to sustained excellence, and lay a foundation for ongoing growth in the state's life sciences industry.

The white paper describes the context for supporting stem cell research at UMass, building on a seed investment of $2.5 million made in 2006. It also outlines a proposed additional investment of $66.4 million to create a system-wide UMass Institute for Stem Cell Research and Regenerative Medicine that would position the University as a leader in the field, build a state-wide research resource, and catalyze industrial collaborations.

## ABOUT STEM CELLS

Stem cells are the precursor cells that serve as the building-blocks for all organs and tissue types. They have a unique capacity to proliferate and become specialized during fetal development to enable tissue and organ formation, and they also serve as a unique reservoir of cells for regenerating damaged or diseased tissue later in life. Understanding and directing their function will create an enormously powerful set of tools for treating and/or curing a broad spectrum of debilitating and life-threatening diseases.

Although there are stem cells that scientists have not yet been able to categorize, there are essentially two types, each of which holds unique value for research and therapy. The first are *embryonic stem cells (ES cells)*. ES cells are derived from the blastocyst, an early stage of development of a fertilized egg, prior to its implantation in the uterus. The blastocyst is a simple ball of primitive cells (roughly 200 in humans), the inner core of which are used to derive ES cells. ES are pluripotent, meaning that they have the ability to give rise to virtually any tissue type found in the body.

While extraordinarily promising, the field of embryonic stem cell research is still very new. Discoveries of ES cells in mice were made in the early 1980s, and human ES cells were only isolated in 1998 at the University of Wisconsin-Madison. Continued progress in ES cell research will require advances in the ability to propagate them and direct them to sites for tissue regeneration and restoration of function of diseased organs.

*Lineage-restricted stem cells*, also called *adult stem cells,* are the second type. They are the intermediate step by which ES cells become specific tissue types. Adult stem cells are found in all organs during early development and in certain organs or parts of the adult body. Their functions include building, maintaining and repairing tissue. Probably the best known example of adult stem cells is hematopoietic stem cells, found in bone marrow, as well as umbilical cord blood and fetal tissue. Hematopoietic stem cells self-renew continuously and are capable of generating any tissue type found in the blood. Discovered in the early 1960s, they have been used in transplant therapy for 30 years.

**THE CONTEXT FOR MASSACHUSETTS AND UMASS**

A global leader in the life sciences on many fronts, Massachusetts institutions received $2.27 billion from National Institutes of Health (NIH) in 2005, trailing only California. We are home to world-class scientists who advance the knowledge base and unparalleled academic and medical centers that train the next generation of life science and healthcare professionals and set the standard for patient care.

The Commonwealth is also home to vibrant life sciences industry clusters in medical devices, pharmaceuticals, and biotechnology, including stem cell and regenerative medicine companies such as Advanced Cell Technology in Worcester, which licenses technology from UMass Amherst. These clusters not only transform knowledge into cures and treatments for patients, but also anchor our innovation economy. A survey by the national Biotechnology Industry Organization identified over 1,300 private sector bioscience entities in Massachusetts, with greater than 50,000 employees. Our economic well-being depends on the growth of innovation industries like the life sciences.

As the Commonwealth's public research university, UMass is uniquely positioned to leverage the scientific and economic development opportunity of the life sciences. The Medical School (UMMS) in Worcester, one of the fast-growing academic health centers in the nation, has world-class programs in gene silencing (led by Nobel Laureate Craig Mello), gene function and expression, growth control, nuclear organization and signal transduction. The cancer, diabetes, musculoskeletal and cardiovascular centers of excellence at UMMS are collaborations between the university and UMass Memorial Healthcare, the medical school's clinical partner. UMMS also anchors Central Massachusetts's emerging biotechnology industry cluster. At the Amherst campus, over one-quarter of the research portfolio is in the life sciences. To expand on those efforts, it has recently forged a partnership with Springfield's BayState Medical Center to create the Pioneer Valley Life Sciences Institute. Contributing research strengths exist at the Boston, Dartmouth and Lowell campuses and can also be developed.

In the area of stem cell research and regenerative medicine, the campuses bring significant resources. UMMS is expanding clinical and translational research with a focus on cardiovascular disease, hematology and oncology and diabetes. Stem cells have been proposed as possible cures for all of these diseases, and research is ongoing in several different areas. Laboratories are investigating issues related to basic cell biology but also emphasize stem cell use in bone disease and blood disorders. With its robust research environment and opportunities for synergies across many fields, UMMS is well-positioned to move new discoveries to development of patient-based therapies. In addition, UMass Memorial manages the state's only public cord blood bank and has a historic commitment to women's and children's health, especially the underserved population of Massachusetts.

At Amherst, animal stem cells have been used for years in its highly-regarded animal genetics, reproduction and immunology programs. Generating cattle by nuclear transplant cloning, one notable achievement in the late 1990s, showed that adult cells can be reprogrammed in the egg to perform as totipotent stem cells. More recently, studies identified a sperm enzyme that unleashes the egg's nuclear reprogramming machinery, creating a novel tool to study reprogramming events and explore generation of animal embryonic stem cells. The Amherst group also works closely with campus colleagues in materials and cellular engineering, also a field of excellence, to develop engineering solutions for large-scale stem cell production for clinical and experimental applications.

## THE NATIONAL COMPETITIVE LANDSCAPE

The federal government has essentially abrogated its responsibility for enabling U.S. leadership in the field of human ES research. In August 2001, the Bush Administration restricted use of federal funds for human ES cell research to 78 cell lines in existence at that time. Scientists subsequently determined that less than one-third (and possibly fewer than 10%) of the cell lines are viable for research and none are suitable for therapeutic use due to contamination. In contrast, over 100 new lines have been derived since then, but they are unavailable under federal grants. Efforts by Congress in 2006 to loosen these restrictions met with a Presidential veto and are expected to fail again this year.

Given this climate, a number of states have taken action. Exercising leadership in a way in which Massachusetts has not yet done, many of our competitors have committed financial resources to their academic and biomedical research institutions for construction and upgrading of capital facilities, hiring of technical staff, and research funding:

- California – an approved $3 billion bond-funded program;
- Connecticut – a $100 million bond-funded program, with initial research awards made in December 2006;
- New Jersey – approved bond-funded programs totaling $500 million ($270 million for research facilities and $230 million for research grants);
- New York – a $1 billion bond-funded proposal by Gov. Spitzer under consideration;
- Wisconsin – a $750 million program for facilities construction and research.

Except for Wisconsin, they are all "leading technology states" against which the Massachusetts Technology Collaborative (MTC) benchmarks our economic performance.

Responding to these challenges requires public and private support. While institutions such as Harvard and MIT will continue using their own funds to implement stem cell research programs, this should not be considered a substitute for the investment of public funds. The ability of UMass to act as an agency of the Commonwealth in support of the state's education, health and economic development objectives creates a unique opportunity. As the Commonwealth's only public university, UMass is able to engage not only students and faculty on a single campus but constituencies across the Commonwealth. By partnering with Worcester-based Commonwealth Medicine, UMass can reach underserved populations, including minority groups. By working with the Massachusetts Biologic Laboratories in Mattapan, UMass is able to produce biologic products, which today include vaccines and monoclonal antibodies, but in the future could include new biologic agents.

## REQUEST BY THE COMMITTEE ON SCIENCE, TECHNOLOGY & RESEARCH

At its August 2006 meeting, the Board of Trustees Committee on Science, Technology and Research instructed the University to develop a strategy for advancing stem cell research. Its guidance was catalyzed in large part by legislative activity over the previous 18 months that focused on 1) creating a regulatory environment to promote human embryonic stem (ES) cell research, 2) the provision of $2.5 million in seed funding to the UMMS and 3) a mandate for the President to submit a feasibility study on a program in regenerative medicine. The charge included the following:

- Outline a system-wide approach to capitalize on opportunities in stem cell R&D, including both human and animal stem cells, ES and adult stem cells, and federally-approved and non-approved human ES lines;
- Identify priorities and opportunities to enable UMMS to maximize impact of the seed funding for the proposed Biomedical Institute for Discovery; and
- Develop an approach that builds on UMMS plans and leverages complementary capabilities at Amherst and other campuses.

A working group was convened, chaired by Professor Robert Finberg of the Department of Medicine at UMMS. A highly regarded scientist, Professor Finberg was appointed by the Governor in 2006 as co-chair of the state Biomedical Research Advisory Committee, which was charged with providing scientific guidance to the Commonwealth in the area of human stem cell research.

Members of the working group presented their plans to the Committee in November 2006. Based on its efforts and the resulting discussion with the Committee, this white paper outlines the opportunity for a system-wide program and a strategy for investment.

## THE UMASS INSTITUTE FOR STEM CELL RESEARCH

The working group proposes creating the UMass Institute for Stem Cell Research, an integrated system-wide program to leverage existing strengths and enhance interdisciplinary research and multi-campus collaboration. The Institute will bring together complementary resources in human and animal stem cell research and capabilities in technology areas such as biological materials, cell engineering and bioinformatics, which are increasingly vital for the life sciences. Working closely with staff from campus technology transfer offices and the Massachusetts Technology Transfer Center, the Institute will also serve as a state-wide resource enabling industry collaborations and supporting entrepreneurship.

### *Governance and Management of Institute*

The Institute will be governed by a Steering Committee of senior faculty members and administrators from the participating campuses (UMMS and Amherst initially, and eventually all the campuses as appropriate) and the President's Office. The primary responsibilities of the steering committee include:

- Identifying for campus leadership on an ongoing basis the priorities for faculty recruitment in stem cell research and regenerative medicine;
- Advising provosts and deans on the allocation of resources to academic units and assists in the selection of new faculty;
- In concert with relevant academic units and research offices, developing guidelines and policies for core facilities to assure quality of operations;
- Conducting outreach to increase access to and enhance use of core facilities by UMass faculty and industry collaborators;
- Reviewing utilization of core facilities and reallocating resources, if necessary, to enhance benefit to the stem cell and regenerative medicine research enterprise of the University and the Commonwealth's life sciences industry;
- Distributing internal grant funding to UMass faculty members to build the University's research enterprise, leverage additional investment, promote industrial collaborations – especially with Massachusetts companies – and promote use of the core facilities;
- Advising campuses on the development and refurbishment of research space.

The working group's faculty members will serve on the steering committee, with Professor Finberg as chair and Dean George Langford of Amherst as vice-chair. Provosts (Amherst and eventually Lowell, Dartmouth and Boston) and the Dean (UMMS) will appoint additional members. Vice provosts/chancellors for research from participating campuses, the UMMS vice chancellor for operations and the Senior Vice President for Academic Affairs, Student Affairs and International Relations and the Vice President for Economic Development (from the President's Office) will serve *ex officio*.

### *Required State Investment*

An investment of $66.4 million[*] over six years would be needed for this activity, broken out as follows:

- *Academic program development ($19.0 million)* – New academic programs will be established at UMMS and Amherst with the recruitment of 15 faculty members.

[*] Excludes $2.5 million provided in 2006.

Funds will also be provided to the Boston, Dartmouth and Lowell campuses to build capacity.

- *Core user facilities ($11.8 million)* – A set of ten core facilities will be developed at UMMS and Amherst and available for use by all UMass researchers. They will also be accessible to investigators from other academic institutions and industry. These facilities will significantly expand research capabilities. The 2006 appropriation of $2.5 million will allow work to start immediately on a human ES cell biology core for federally-approved lines, (UMMS), a gene silencing core (UMMS), and an animal stem cell core (Amherst). To fully leverage existing strengths, some cores may be jointly sited at both campuses.
- *Research program development ($7.1 million)* – The Institute will have discretionary funds to support the development of research programs and promote industrial collaborations. These funds will also be used to support the integration of activities at Boston, Lowell and Dartmouth.
- *Facility renovation and construction ($28.5 million)* – UMMS anticipates the need for a new 30,000 $ft.^2$ facility in which to perform research using human ES cell lines which are not approved by NIH under existing federal regulations. Amherst expects to renovate and add modular space to existing buildings totaling 12,000 $ft.^2$.

***Academic Program Development***

If the Commonwealth is to compete successfully to build and retain knowledge institutions, the recruitment of talented, world-class researchers must be the centerpiece of its strategy. This is equally true of its academic institutions as its companies. UMass is building a track record of successful research program development in a number of fields – nanotechnology, computer science and networking, polymers and materials, gene silencing – and is well-positioned to do so in stem cell research.

At UMMS, a new academic program of stem cell biology and regenerative medicine will be established through the recruitment of ten new faculty members. The department will focus on basic biological issues that constitute the current roadblocks to continued advances and stem cell-related therapies. This investment will not only augment current research strengths in other departments where stem cell programs are under way (especially hematopoietic, neuroscience and orthopedic research), but will also leverage the school's emerging emphasis on clinical and translational science, i.e., moving scientific discoveries rapidly from the laboratory though to approved therapies for patients. An investment of $12.5 million is budgeted for recruitment, start-up and departmental program development.

Amherst will establish an academic program in stem cell research involving the Colleges of Engineering, Natural Resources and the Environment and Natural Sciences and Mathematics. An investment of $5.5 million will target recruitment of five new faculty members in key areas. The campus, in close consultation with the steering committee, will develop a strategy for continuing to build expertise across a number of fields, including animal and veterinary science, engineering, biology and bioinformatics. Recruitment of faculty will be closely aligned with development of core facilities.

### *Core User Facilities*

Shared, centrally-managed core user facilities will provide UMass investigators access to tools, specialized capabilities and technical support. The cores will also serve as a state-wide resource, available to other academic and industry researchers and enabling collaboration. Each core will receive an equipment/start-up investment of $500,000 in its first year and annual operational support of $150,000 for five years.

Initially, the Institute will devote its efforts to bring on-line cores in areas where the campuses already have significant operations and research expertise: *human ES cell biology*† and *gene silencing* at UMMS, and *animal ES biology* at Amherst. Over time, additional core facilities will be established at both campuses. Three new cores will be created at UMMS: *proteomics and protein fractionation, microarray technology*, and *gene sequencing and synthesis*. Three new cores will be established at Amherst: *cell materials interface, cell engineering* and *imaging*. Two new cores will be sited at both campuses: *chemical biological screening* and *bioinformatics and computational biology*.

*Human Embryonic Stem Cell Biology Core (Worcester)*

This core facility will provide human ES cells to researchers at UMass for investigation of biological control and therapeutic application and will work with them to develop human embryonic stem cell-based approaches for fundamental biological and clinical applications. The capabilities and resources of the core will provide UMass investigators enhanced credentials in human embryonic stem cell research for highly competitive NIH-based support and funding from the private sector.

There will be stringent quality control and characterization of the cells, employing existing routine procedures, to ensure that the human ES cells are competent to support specialized functions in response to physiological cues. Stock cultures and cells will be karyotyped to establish retention of the diploid state and cytogenetically screened for chromosomal abnormalities that include deletions, amplifications or translocations. DNA sequencing will be carried out if necessary. Expression of stem cell markers (e.g. OCT1) will be verified by immunohistochemistry. The ability of human embryonic stem cells to differentiate along the principal tissue lineages will be monitored. Focusing initially on federally-approved cell lines, the core's activity will be expanded once appropriate facilities are in place to manage cell lines derived after August 2001.

*Animal Embryonic Stem Cell Biology Core (Amherst)*

Utilizing techniques used in the Department of Veterinary and Animal Sciences, high-quality, tested, ES cell lines from various mouse genetic backgrounds will be made available to investigators at UMass and to partners. These cell lines will support basic and applied research on stem cell development and differentiation. The goal of the core is to facilitate improved understanding of processes that regulate the development and

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† This facility will receive $300,000 annually for operational support.

differentiation of stem cells in non-primate models, with a view towards using this knowledge to improve human stem cell line development and growth *in vitro* and *in vivo.*

In addition, the core will generate, bank and make available to investigators high quality, tested, ES cell lines from companion animals and livestock species. These will support veterinary clinical applications and the development of stem cell based therapies.

The core will work with investigators to develop collaborative projects that utilize core technologies to evaluate effects of specific gene silencing or over expression on blastocyst/ES cell line/embryo/tissue development in the mouse and other mammal species. This core function will include the generation of ES-like stem cells tailored to the needs of individual animals using the reprogramming power of the egg cytosol.

*Gene Silencing Core (Worcester)*

This core will have two basic functions: serving as an siRNA/shRNA repository accessible by investigators and performing loss-of-function genome-wide screens that would otherwise be beyond the budget and technical capabilities of most laboratories.

By obtaining human and mouse genome shRNA and siRNA libraries, the core's reagents will be made available to investigators as individual clones or whole/partial libraries. The core will also work with individual scientists to design and carry out genome-wide screens using these libraries. In this manner, the core will provide investigators with rapid access tools enabling them to silence genes of interest economically and rapidly, making their projects significantly more competitive for federal support.

In performing loss-of-function genome-wide screens, the core will enable scientists to design cell-based assays and then examine all genes for ones, which when silenced, affect the biological process of interest. This will be powerful genetic approach to advance science and is expected to generate considerable intellectual property. As a unique core not available elsewhere, it will give UMass investigators and partners a competitive advantage. Unlike a screen for a small molecule that may interfere with a biological process but where the target of the small molecule remains to be identified, an interfering shRNA/siRNA immediately identifies the target gene/protein. The opportunity for important discoveries and scientific contributions is thus magnified.

*Proteomics & Protein Fractionation Core (Worcester)* – Utilizing extensive mass spectrometry services for analysis, the core will provide the preparative and analytical expertise and tools that can help researchers determine how individual proteins change in different cell types or from normal tissue to disease.

*Microarray Core (Worcester)* – This core will provide cost-effective, time-efficient access to microarray technology and an environment that facilitates effective analysis and sharing of microarray data compiled for research purposes; allows scientists to survey the expression of thousands of genes at one time and to compare multiple samples.

*Sequencing & Synthesis Core (Worcester)* – The focus of this core will be to synthesize custom oligonucleotides and peptides, providing investigators with a resource to build any of the millions of tiny fragments of DNA or proteins necessary to undertake investigations in stem cell research programs. UMMS's state-of-the-art DNA sequencing capabilities will expand to accommodate rapidly-evolving needs for genomic analysis.

*Chemical Biology Screening Core (Worcester & Amherst)* – This core will employ the chemical sciences to understand the principles that underlie biology and to develop approaches to ameliorate disease. Key themes include high-throughput screening, chemical synthesis tools, chemoinformatics tools and databases, techniques for target identification and molecular imaging techniques.

*Bioinformatics and Computational Biology Core (Worcester & Amherst)* – There are two components to the core; the bioinformatics program will mainly provide a *service* role to investigators, while the computational biology program will support *collaborative research*. Bioinformatics component will provide the underlying software, hardware, and networking "glue" to manage biological data. Computational Biology will involve the application of statistical and model-driven techniques for the analysis of often complex, integrated, and high dimensional data sets. Emerging techniques in computer science will be emphasized. Required infrastructure includes augmentation of existing computational biology cluster at Amherst.

*Cell-Materials Interface Core (Amherst)* – The goals of the core will be to develop polymers that are compatible with living cells and promote tissue development from stem cells. The highly functionalized, innovative polymers will be used to coat surfaces so that the interface between living cells and artificial surfaces become seamless. The development of new materials that are cell-tolerant and have the ability to deliver signals to cells will create a fundamental change in the paradigm of regenerative medicine. The core will generate these materials for investigators requiring stem cells for studies of cell growth and tissue development.

*Imaging Core (Amherst)* – The imaging core, by developing and refining an array of techniques, will provide capabilities to accelerate discovery and promote synergies for both human and animal stem cell programs. Advanced imaging techniques will expedite stem cell isolation and characterization, support analysis of interactions between molecules that regulate stem cell development and differentiation, enable harvesting of stem cell from defined tissue regions for genomic analysis, and provide real time *in vivo* analysis of transplanted stem cell and their progeny.

### *Research Program Development*

In addition to recruiting additional faculty members to work in the area of stem cell biology, the Institute will support the development of new initiatives by providing seed funding for projects that can ultimately obtain their own support. A steering committee consisting of representatives from each campus will screen proposals from faculty members on all campuses. Collaborations between different campuses, as well as collaborative ventures with industry will be encouraged. It anticipated that at least two projects will be supported every six months for the first five years of the program. Priority will be given to innovative projects in any area of stem cell biology that involve multi-campus or campus-industry collaborations. Support will be given for no more than three years to encourage the investigators to obtain their own funding.

### *Facility Renovation and Construction*

Given current federal restrictions, significant additional infrastructure will be required to make progress in research and development of therapies using human embryonic stem cells. In order to expand its programs, UMMS will build a new 30,000 $ft.^2$ (gross) research center devoted to non-federally-approved human ES lines, which present the greatest opportunity for advances. It will be a state-of-the-art facility that will support the faculty and related science cores (described above) and technology required to maintain and enhance stem cell research growth and discovery.

UMMS has extensive experience with designing and building effective and efficient research space that can accommodate changing technology and support needs, and the new facility will provide over 20,000 $ft.^2$ of flexible wet lab and lab support space. The cost is projected to be approximately $20 million broken out as follows: $12 million for shell and core ($400 per $ft.^2$), $5 million for interior fit-up ($167 per $ft.^2$) and $3 million for furniture, fixtures and building equipment ($100 per $ft.^2$).

Amherst plans to add 12,000 $ft.^2$ of new and renovated laboratory space. Two modular units will be added to the main laboratories of Veterinary and Animal Sciences to house the animal stem cell and imaging cores and will accommodate a new faculty hire with a programmatic focus on mechanisms of somatic cell nuclear reprogramming aimed at the conversion of normal differentiated body cells into stem cells in a test tube.

Modular units will also be added to laboratories in Computer Science and Chemical Engineering and additional space will be renovated. The new and renovated structures will accommodate four new faculty members who will direct the chemical biology screening, bioinformatics and computational biology, and cells-materials interface cores. These improvements are planned for adjacent buildings, which will expedite close interactions among the faculty who manage and use the cores.

## CONCLUSION

Scientists in the Commonwealth, both in academia and industry, are well positioned to take advantage of future developments in stem cell research. By combining the resources available at its Worcester and Amherst campuses, UMass is currently developing resources that will support the growth of research in stem cells and regenerative medicine. Using the talents of the investigators at all its campuses, UMass can be a major force in both discovery and, later, in the use of this technology to treat patients. Investments in this area are likely to lead to the creation of new jobs in the short term, and in the long term, investments in this area may have a major effect on improving the health of the people of the Commonwealth.