BY KIM RIBBINK

STEM CELLS

The Stem of Hope

New findings and understandings about the way stem cells operate and their potential in therapeutic development **HAVE LED TO REAL HOPE THAT THERE COULD SOON BE TREATMENTS FOR LIFE-THREATENING DISEASES**. Experts in the field discuss the milestones that have been achieved and the implications for stem-cell therapeutics.

It's been a significant year for stem-cell research, both in the laboratory and in the corridors of government.

Stem-cell research, a field that encompasses a broad range of disciplines, from blood-cord to adult stem-cell lines to somatic stem-cell research to embryonic stem-cell research, has exhibited some significant results in the pursuit of life-saving and life-enhancing products and treatments.

Investigations into the potential to treat disorders with stem-cell derived products are burgeoning; a database of NIH-sponsored clinical trials, clinicaltrials.gov, shows 800 studies in progress.

"These are exciting times for stem-cell research, and with new discoveries surfacing every day, companies small and large are playing pivotal roles in shaping the impact of regenerative science and medicine on the lives of millions of people around the world, from the perspective of life expectancy and the quality of life," says Mercedes Walton, chairman and CEO of Cryo-Cell International Inc., one of the world's largest cord blood banks.

The financial potential of stem-cell research also is growing rapidly. According to a report by RRY Publications titled Stem Cell Analysis and Market Forecasts 2006-2016, stem-cell company revenue is predicted to grow from $974,000 in 2005 to $8.5 billion in 2016. There are currently more than 200 companies worldwide developing stem-cell products.

Politically speaking, the area of human embryonic stem cell (hESC) research has generated the most controversy, drawing opposition from religious leaders and social conservatives over the use of human embryos.

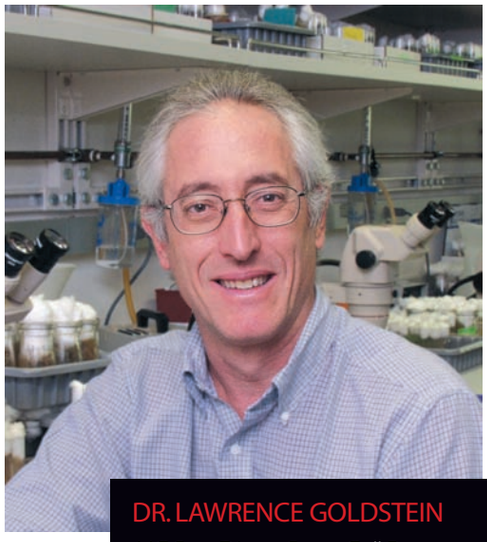
While President George W. Bush vetoed a bill in June of this year to permit federal funding of hESC research, a number of states — such as California, Connecticut, Maryland, New Jersey, New York, and Wisconsin — have been forging ahead in an effort to attract researchers and be at the forefront of research. Additionally, Massachusetts is pushing forward with its own efforts; Governor Deval Patrick is seeking to lure biotech scientists to his state with a proposed $1 billion package over 10 years, including support for embryonic stem-cell research.

Across the stem-cell world, there is much excitement and hope, as well as ongoing questions as to how the technology will develop into therapeutics to treat patients.

"In the world of stem-cell therapeutics, there has been some maturation of the technology and simultaneously there has been greater understanding by the regulatory community about how these products will be deployed clinically," says Robert Hariri, M.D., Ph.D., CEO of LifebankUSA and Celgene Cellular Therapeutics. "As a result, these products are being developed much like pharmaceutical products; they're being held to high standards of quality and consistency, and they are being looked at critically in terms of how they will be delivered to patients, how their effects will be monitored, and how surveillance programs will be built to make sure they do what we think they should."

EARLY PROMISE

With growing knowledge and insight into stem cells and their capabilities come excitement about their potential to treat multiple conditions.



DR. LAWRENCE GOLDSTEIN
UC San Diego Stem Cell Program

WITH THE STEM-CELL INITIATIVE IN CALIFORNIA COMING OUT OF COURT, there's going to be substantially ramped-up investment in the sciences in the state and, hopefully, that will continue to spur the federal government, other states, and other nations to increase their financial investment, not only in stem-cell research but in science in general.

A unique property of stem cells is their ability to act as a dual therapeutic platform, since the cells being delivered from a donor to a recipient act both as a graft material and as discrete biologic response modifiers.

"When stem cells are put into a recipient, they release small molecules that change the environment in a proactive way," Dr. Hariri says. "As a result, early progress is likely to be in the ability of stem cells to act as a modifier of a host's immune system. I think stem cells will earn their wings in the clinic, first and foremost, in autoimmune diseases — such as rheumatoid arthritis, multiple sclerosis, and Crohn's disease — where a patient's dysfunctional immune system begins to attack itself."

Because of the potential risks in clinical research, Lawrence S.B. Goldstein, Ph.D., investigator, Howard Hughes Medical Institute, professor of the Department of Cellular and Molecular Medicine, and director of the UC San Diego Stem Cell Program, believes early targets will likely be disorders that are rapidly fatal. These include Lou Gehrig's disease or amyotrophic lateral sclerosis (ALS), a fatal neuromuscular disorder; Batten disease, or neuronal ceroid lipofuscinosis (NCL), a fatal, inherited disorder of the nervous system; and aggressive forms of cancer.

"With Lou Gehrig's disease there's a lot of interest in developing stem-cell approaches, and a number of groups are starting to develop methods for transplanting stem-cell derived cells into the spinal cord of animal models," Dr. Goldstein says.

In his own research at UCSD, Dr. Goldstein and his colleagues have been working to develop methods using hESCs to develop true human models of Alzheimer's disease to test hypotheses and ideas that have come from studies on animals.

E. Edward Baetge, Ph.D., chief scientific officer of Novocell Inc., believes the first potentially successful trials in humans will be those focused on neural stem-cell repair of the nervous system that require smaller numbers of cells and may be more easily grafted without heavy immunosuppressive regimes.

An example is Stem Cell Inc.'s Phase I clinical trial of its proprietary HuCNS-SC product candidate (purified human neural stem cells) as a treatment for infantile Batten disease.

"So far these trials have demonstrated early safety at the lowest grafted cell dose in three patients," Dr. Baetge says. "I believe other trials such as those planned by Geron for spinal cord injury using hESC derived oligodendrocytes and in the future for age-related macular degeneration using hESC-derived retinal pigment epithelium by Advanced Cell Technology hold promise."

THERAPEUTIC **POTENTIAL**

Elsewhere, developments in the area of cancer stem cells are paving the way for novel oncology therapies. Ian Phillips, Ph.D., DSc,

Experts

E. EDWARD BAETGE, PH.D. Chief Scientific Officer, Novocell Inc., San Diego; Novocell is a stem-cell engineering company dedicated to creating, delivering, and commercializing cell and drug therapies for diabetes and other chronic diseases. For more information, visit novocell.com.

LAWRENCE S. B. GOLDSTEIN, PH.D. Investigator, Howard Hughes Medical Institute, Professor, Department Of Cellular and Molecular Medicine, Director, UC San Diego Stem Cell Program, San Diego; The mission of the Department of Cellular and Molecular Medicine is to support and promote research and teaching in molecular cell biology in the School of Medicine at UCSD. For more information, visit tcmm.ucsd.edu.

ROBERT HARIRI, M.D., PH.D. CEO, LifebankUSA and Celgene Cellular Therapeutics (CCT), Summit, N.J.; LifebankUSA is a subsidiary of Celgene Corp., an integrated biopharmaceutical company engaged in the discovery, development, and commercialization of innovative therapies designed to treat cancer and immunological diseases through regulation of genomic and proteomic targets. For more information, visit lifebankusa.com and celgene.com.

JOHN LEWICKI, PH.D. Senior VP, Research and Development, OncoMed Pharmaceuticals Inc., Redwood City, Calif.; OncoMed is discovering and developing novel therapeutics targeting cancer stem cells, the cells believed to be capable of driving tumor growth, recurrence, and metastases. For more information, visit oncomed.com.

IAN PHILLIPS, PH.D., D.SC. Norris Professor of Applied Life Sciences, Biology of Stem Cells, the Keck Graduate Institute of Applied Sciences (KGI), Claremont, Calif.; KGI is the only American graduate institution devoted solely to bioscience education and discovery. For more information, visit kgi.edu.

MERCEDES WALTON. Chairman and CEO, Cryo-Cell International Inc., Oldsmar, Fla.; Cyro-Cell's primary focus is on the cryopreservation of umbilical cord stem cells for family use. For more information, visit cryo-cell.com.

Norris Professor of Applied Life Sciences, Biology of Stem Cells, at the Keck Graduate Institute, says the identification of pancreatic cancer stem cells by researchers from the University of Minneapolis opens the possibility of attacking pancreatic cancer.

One company, OncoMed Pharmaceuticals Inc., has been focusing on how knowledge about cancer stem cells may offer insight into improving the way cancer is treated.

"We think that cancer stem cells (CSCs) are derived from normal adult stem cells or early progenitor cells," says John Lewicki, Ph.D., senior VP for research and development at OncoMed. "These cells have the ability to self-renew and as such have the ability to fuel the growth proliferation and metastasis of solid tumors. We think these cells, which are potently tumorigenic, are the cells that are responsible for spreading cancers to distant sites."

OncoMed has begun preclinical development on identifying monoclonal antibodies and small molecules that are capable of eliminating CSCs involved in the formation and growth of solid tumors.

To date, OncoMed has tested about 150 antibodies in xenograft models derived from CSC-driven human tumors and identified a number of antibodies with reproducible anti-tumor activity. In its most advanced project, the company has discovered an antibody that binds with high affinity and selectivity to its target and functions to completely block ligand-receptor binding and subsequent signaling in CSCs. This antibody has shown activity in a variety of tumor models, both as a single agent and in combination with approved cancer treatments. OncoMed has humanized this antibody successfully and is proceeding with manufacturing clinical material and IND-enabling studies.

Ms. Walton says areas that have the broadest potential benefit, such as diabetes, neurological disorders, and heart disease, offer the best near-term promise.

"Research in these areas has progressed beyond the lab and into clinical studies, showing promising early results," she says. "For example, several clinical studies are currently exploring the application of stem cells to repair damaged heart muscle tissue or blood vessels in heart attack patients; to treat diabetes by creating insulin-producing cells; and in neurological therapies such as Parkinson's disease, spinal cord injury, and multiple sclerosis."

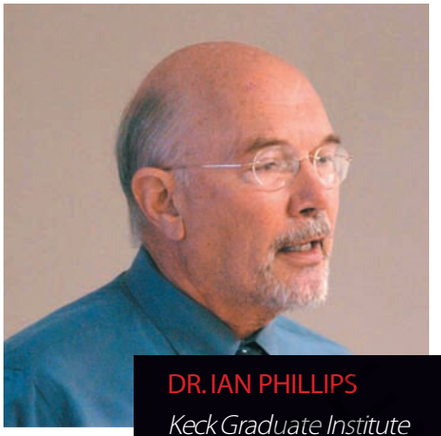
Another area of stem-cell research that is being investigated for therapeutic development is mesenchymal stem cells (MSCs), which are multipotent stem cells that differentiate into a variety of cell types. Applications of MSC engraftment/transplantation may improve a variety of degenerative conditions because of MSC's generalized ability to differentiate into fat, bone, cartilage, and endothelial cell precursors, Dr. Baetge says. This offers promise for endogenous tissue repair and regeneration.

Osiris Therapeutics is one of the most prominent companies in the area of MSC research, Dr. Baetge says. The company has found that MSCs are generally not rejected by the host immune system. This unique feature eliminates the need to tailor MSCs based on donor matching and may mean that patients can forgo the side effects of immune suppression.

Osiris has a fairly broad pipeline in MSC research. The company is evaluating the use of Prochymal to treat Graft versus Host Disease (GVHD), a life-threatening immune condition, in a multicenter Phase III clinical trial. Osiris also is evaluating Prochymal for the treatment of Crohn's disease and has completed enrollment in a Phase II clinical trial.

Osiris also is evaluating Provacel, a formulation of stem cells to repair damaged heart tissue following heart attack, and has completed enrollment of a Phase I clinical trial.

Additionally, Osiris has completed enrollment of a Phase I/II study for Chondrogen, an injection of stem cells formulated to repair damaged tissue in the knee joint and prevent the progression of arthritis.



DR. IAN PHILLIPS
Keck Graduate Institute

THE BIGGEST STUMBLING BLOCKS IN STEM-CELL RESEARCH ARE THE CAUTIOUSNESS OF BIG PHARMA to get into stem-cell therapies and a lack of venture capital investments.

HOLD UPS AND **PROGRESS**

With the progress Osiris is making, Dr. Baetge says it could be between two and four years before the company submits a BLA for the Phase III clinical candidates.

The near future promises a wealth of IND filings, Dr. Hariri says, with many more products entering the clinic over the next two to three years.

Some difficulties, however, continue to stymie research and development. Ms. Walton says a big challenge has been that the most valuable cells that are highly prolific, undiffer-

Stem-Cell Facts

CURRENT APPLICATIONS FOR STEM-CELL PRODUCTS

- Replacement for bone harvesting in spine fusion surgery
- Bone growth and void fill in fresh fractures
- Bone growth and void fill in non-union fractures

STEM-CELL PRODUCTS EXPECTED TO BE APPROVED BY THE FDA IN THE COMING 36 MONTHS

- Prochymal (treatment for graft vs. host disease)
- Two (possibly three) treatments for damaged heart muscle due to heart disease
- Chondrogen (repair of knee cartilage)

MARKET FOR STEM-CELL PRODUCTS

- Patient population in the United States for whom existing stem-cell therapies are applicable: more than 2.5 million
- Number of patients treated in 2006 in the United States with stem-cell products for orthopedic, cardiovascular, dental, aesthetic, oncologic, or other indications: 5,900
- Market value of all public stem-cell companies: $1.66 billion
- The most common type of commercial stem cell: an adult stem cell derived from bone marrow

Source: Stem Cell Analysis and Market Forecasts 2006-2016, by Robin R. Young, Founder and President, RRY Publications LLC, Wayne, Pa. For more information, visit ryortho.com.

MERCEDES WALTON
Cryo-Cell International

IT IS IMPORTANT TO KEEP IN MIND THAT REGENERATIVE MEDICINE IS A RELATIVELY NEW AREA OF RESEARCH, and as such the technology within the scientific and medical communities is in a proof-of-concept phase.

entiated but without the propensity to form cancer are not readily accessible.

"Another key issue relates to immunological challenges inherent with stem cells," she says. "Specifically, there is a risk of the body rejecting transplanted cells from a donor other than the recipient."

Uncertainty among regulatory bodies over safety profiles will be a roadblock, at least until stem cells from a number of sources have found their way into the clinic and there's been a demonstration of uniform safety across the board, Dr. Hariri says.

For many, the controversy over hESC research remains a cloud over the field that has the potential to affect all areas of research.

"Since no area of science operates alone, the breakthroughs that would come from research in areas that are not politically popular or are politically controversial means science is missing the opportunity to contribute to the other areas," Dr. Goldstein says.

It is also the activity itself that is important for progress, he notes.

"Science requires the integration of methods and ideas from a variety of different approaches to solve problems," he says. "When one area of technology that has tremendous promise is artificially limited primarily because of political issues it throws things out of balance, and research misses what could be done there."

In an effort to address some of the concerns about embryonic stem-cell research, the International Society for Stem Cell Research (ISSCR) has released its Guidelines for the Conduct of Human Embryonic Stem Cell Research, calling for special scrutiny of human embryonic stem-cell research and specifying rigorous ethical standards for scientists working with human embryonic stem cells, seeking to promote responsible, transparent, and uniform practices worldwide.

The importance of human embryonic stem cells lies in their pluripotency, since pluripotent stem cells can give rise to any type of cell in the body except those needed to develop a fetus.

Experts say stem cells derived from discarded placental tissue or from amniotic fluid harvested from routine procedures offer an alternative to the more controversial hESCs.

Celgene's platform has been focused on placental-derived stem cells (PDSCs), and Dr. Hariri says they have been shown to offer a strong alternative solution to some of the hurdles. These include finding stem cells that can regenerate tissue, that overcome immunological barriers between donor and recipient, that don't raise public objections, and that are readily available and economic.

"PDSCs solve those issues because the leftovers from birth are readily available; they are economical since the mass of cells recovered from a single placenta is many log orders greater than the number of cells that can be derived from the fetal embryo; and the immunological barrier is overcome because of the unique properties of the placenta, meaning the cells can likely be delivered from one placenta to any recipient without being rejected," he says.

Another area of concern lies in the area of the safe conduct of clinical trials and building greater safety controls from the outset.

But Dr. Hariri says there are strong safeguards in place.

"The regulatory world has imposed very high standards to ensure that the products are what the companies say they are and that there are systems in place to ensure that when they're released for clinical trials, and ultimately for commercial use, standards will be met," he says.

MORE INVESTMENT INTO EARLY-STAGE STEM-CELL COMPANIES — those focused either on adult or embryonic stem cells — would accelerate translation of this new science into clinical trials with product potential.

DR. EDWARD BAETGE
Novocell

DR. ROBERT HARIRI
Celgene Cellular Therapeutics

Reservations over the use of human embryos in stem-cell research **HAVE CREATED STRONG INCENTIVES TO FIND ALTERNATIVES OR SOLUTIONS** to embryonic stem cells.

CLEARING THE PATH

As in any area of research, the underlying issues of resources and talent remain two of the biggest impediments to advancement. In stem-cell research, these challenges have been exacerbated by political wrangling.

"Having a federal government that has allowed politics to tangle up its science policy is a real problem because it hampers the use of federal money," Dr. Goldstein says.

According to Dr. Phillips, money from NIH funds is critical for academic research, which in turn becomes vital to young biotech companies that can translate the research into products to help people.

"Without NIH funding, academic research becomes more difficult, creating a bottleneck in the traditional system of drug discovery and development," he says.

Nevertheless, there have been some important developments that offer hope and promise to research.

In May, the California Supreme Court ruled that the California Institute of Regenerative Medicine (CIRM) may begin distributing grants for stem-cell research. The ruling upheld a decision of a lower state court on the constitutionality of Proposition 71, which was approved by California voters in 2004 to support stem-cell research with more than $3 billion in bond funds. The ruling means funds can be distributed to researchers in California.

"In today's climate where there is a lack of federal funding for stem-cell research, California is leading the way to ensure that stem-cell science is advanced and translated into therapies for people impacted by diseases," Dr. Phillips says.

Equally, though, there is a need for private money to be invested in research and for pharma to shake off its reluctance to get into stem-cell therapies, experts say.

Ms. Walton says in the area of research Cyro-Cell has focused on the most — cord blood stem cells — there has been a groundswell of support and investment in recent years.

Of significance with regard to cord blood stem-cell research is legislation passed in 2006 on public cord blood banking, expanding the number of public cord blood banks in the United States and increasing awareness about the benefits of cord blood preservation.

"Since the first cord blood transplant in the 1980s, cord blood stem cells have been used in more than 7,000 transplants worldwide to effectively treat more than 70 life-threatening diseases and conditions," Ms. Walton says.

Scientific progress in all areas depends on the sharing of ideas. In its guidelines, the ISSCR notes that when it comes to international collaborations, issues over ownership of intellectual property rights will arise. The organization has said in general it stands for the open exchange of scientific ideas and materials to maximize exploration, to promote innovation, and to increase the probability of public benefit through affordable advances made possible by human stem-cell research.

How patents affect research, therefore, also remains key. Dr. Baetge says the challenge levied by the California Taxpayers Association against the original patents held by WARF (Wisconsin Alumni Research Foundation) on patents for human embryonic stem cells is significant.

"This challenge has resulted in a USPTO re-examination of the validity of the WARF patents in light of previously published data," he says.

In the future, a central element to developing stem-cell therapeutics is understanding the unique properties of the cells.

"One area we're looking into is how these cells synthesize proteins in response to different conditions and how they respond to different chemical cues in their environment, and this understanding is critical to making these products a long-term player in medicine," Dr. Hariri says. ✦

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

U.S. Stem-Cell Therapy Market

2005-2016		
Year	**Annual Sales**	**Estimated Growth**
2005	$0.9	—
2006	$16.4	1,722.8%
2007	$36.9	124.7%
2008	$146.1	296.4%
2009	$303.5	107.8%
2010	$707.3	133.1%
2011	$1,331.5	88.2%
2012	$2,335.1	75.4%
2013	$3,422.5	46.6%
2014	$4,741.5	38.5%
2015	$6,346.6	33.8%
2016	$8,476.8	33.6%

Note: Dollars in millions

Source: Stem Cell Analysis and Market Forecasts 2006-2016, by Robin R. Young, Founder and President, RRY Publications LLC, Wayne, Pa. For more information, visit ryortho.com.

Medidata Rave

Works on any computer

Through any browser

In any language

For EDC and CDM

And it's a snap to learn.

Tasmania, Siberia, Timbuktu.

The complete solution for anywhere your clinical research takes you.

medidata®

Medidata Solutions Worldwide

Technology for a healthy world.™

www.mdsol.com

1.212.918.1847