Is Determined To Get Its Products To Market

Twenty-year-old stem cell research firm Aastrom Biosciences (NASDAQ CM-D:ASTM, Ann Arbor, Mich.) continues to fight its way to the marketplace, despite some body blows — NASDAQ delisting, FDA clinical hold on a critical human trial — that might have staggered less resolute companies.

There has been some good news recently.

NASDAQ, for example, notified the company on March 23 that it was once again suspending enforcement of rules requiring a minimum $1.00 a share closing bid price and a minimum market value of publicly held shares until July 20, 2009, because of “continued extraordinary market conditions.” (Aastrom’s shares closed at 40¢ on March 20.)

This can be construed as good luck — if “extraordinary market conditions” can be called a fortunate circumstance — because the company was first notified it was in violation of the rules back in December 2007, and has received several extensions since then.

It means that Aastrom still has access to a public market for trading of its shares, even though its primary source of cash has been an agreement with Fusion Capital Partners, a broad-based investment fund.

On the clinical trial front, the U.S. Food and Drug Administration early in March released the clinical hold on the company’s Phase II trial for dilated cardiomyopathy, a form of heart failure. It began enrolling patients in October 2008. The trial was suspended in February 2009 when one of the participants suffered a “serious adverse event.” Two separate investigations later determined that the problem had to do with anesthesia administration, and had nothing to do with the surgical administration of Aastrom’s cells or with the

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cells themselves.

But the good news tells only a small part of the story of Aastrom, which seems to be yet another small company that has become flotsam on the turbulent global financial seas, buffeted by forces beyond its control.

**On The Plus Side: A Feasible Technology And Clinical Trials In The Works**

Aastrom’s strategic plan is based on the future success of its proprietary technology: Tissue Repair Cells.

TRC technology may not be as headline-grabbing as human embryonic stem cell (hESC) or induced pluripotent stem (iPS) cell technology, but that doesn’t mean it has any less potential for therapies. And early data from small clinical tests bears that out (see below).

The technology combines a proprietary cell manufacturing platform system with what Aastrom calls “Single-Pass Perfusion” (SPP) technology. SPP controls gas and cell culture media exchange to enable the replication of early-stage stem and progenitor cells while preventing their differentiation into mature cells.

The process begins in the clinic, with the removal of a small sample of bone marrow from the patient’s hip in an outpatient surgical procedure.

The sample of bone marrow is shipped to Aastrom’s manufacturing facility, and transferred into its cell manufacturing system.

The automated, sterile manufacturing process greatly expands the stem and progenitor cell populations present in the bone marrow to yield cellular products based on the Tissue Repair Cell (TRC) technology.

The finished TRC-based product is shipped back to the physician who administers it to the original patient as an autologous cell therapy.

A major advantage of this process is that it uses the patient’s own (autologous) cells. There is no risk of immune suppression caused by the introduction of allogeneic (someone else’s) cells.

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The company at one time had four off-shoots of its TRC technology, each targeting specific tissues: the heart (Cardiac Repair Cells, or CRCs), blood vessels (Vascular Repair Cells, or VRCs), bone tissue, (Bone Repair Cells, or BRCs), and nerve tissue (Neural Repair Cells, or NRCs).

CRCs are being tested clinically in the United States and Germany on dilated cardiomyopathy patients; VRCs are being tested clinically in the United States and Germany on critical limb ischemia patients.

The company launched a clinical trial of its bone tissue product (BRCs) in the United States and Spain on patients with osteonecrosis of the femoral head (the round ball at the top of the femur that inserts into the pelvic socket.) Osteonecrosis results when bone tissue lacks a blood supply and eventually dies.

Unfortunately, two of its TRC development programs were suspended for economic reasons.

Aastrom discontinued the BRC trial in May 2008 because of funding problems. It has no plans to revive the research unless its cash situation improves.

As for the NRC development initiative, the company has no plans to launch human trials, again unless it is able to shore up its funding situation.

With the discontinuance of the BRC and NRC programs, the company is putting all of its product development eggs into the CRC and VRC programs.

The company believes these two programs are the furthest along developmentally, and therefore closest to reaching the marketplace, and they probably have the greatest clinical and market potential.

Now that the FDA has lifted its clinical hold on the IMPACT-DCM cardiac cell trial, patient enrollment will resume at the four initiated clinical sites. (These include the Methodist DeBakey Heart & Vascular Center (Houston, Texas), Baylor University Medical Center (Dallas, Texas), and the University of Utah School of Medicine (Salt Lake City, Utah).

So far, nine of 40 patients have been enrolled in the IMPACT-DCM trial at the first three sites. A fourth site, the Cleveland Clinic Heart and Vascular Institute (Cleveland, Ohio), was recently initiated and trained for participation in the IMPACT-DCM trial.

Activation of a fifth clinical site is underway, the company said.

In October 2008, the company enrolled the first 30 patients in RESTORE-CLI, a U.S. Phase IIb clinical trial to test the safety and effectiveness of its TRC treatment for patients suffering from critical limb ischemia (CLI), the end stage of peripheral arterial disease. Since then, another 21 patients have been enrolled at a total of 21 clinical sites.

**Clinical Trial Outlook**

Aastrom is obviously pinning its hopes on the success of both the IMPACT-DCM and RESTORE-CLI trials.

Successful outcomes in these trials would go a long way toward persuading potential funding sources that Aastrom’s technology and products have a shot at succeeding in the marketplace and providing a return on investment.

The company already has some encouraging signs of potential success, however.

**Early Success With DCM Treatment**

In April 2008, Aastrom reported data from two “compassionate use” patients treated in Germany with our autologous stem cell therapy for DCM.

“Compassionate use” is a way to provide experimental drugs or treatments before a regulatory authority, such as the FDA, gives its final approval for use in humans.

The procedure is reserved for use with very sick patients who have no other treatment options.

The FDA often acts on a case-by-case basis when approving “compassionate use” of a drug or therapy.

In the case of Aastrom’s CRCs, the com-

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pany reported that a cardiothoracic surgeon at the University Hospital in Düsseldorf (Germany) performed the first human application of the company’s CRC product.

The surgeon, who is experienced with cell therapy, injected the cells directly into the heart muscle during open heart surgery for these two patients in late 2007.

The data from the two critically ill patients upon discharge from the surgical center was encouraging, Aastrom reported.

The patients were released from the surgical center and then followed by regional rehabilitation hospitals or local physicians.

One patient’s condition improved significantly over the course of two months. However, the patient decided eventually to discontinue his treatment and, against doctor’s recommendation, left the hospital. He subsequently died of natural causes not related to the cell therapy.

The second patient also showed significant improvement seven months after treatment. Experience with this patient helped Aastrom get its Phase II IMPACT-DCM trial approved in the United States.

**Early Success With CLI Treatment**

More encouraging clinical results came in the form of data from tests of the Vascular Repair Cells (VRC). Positive interim results were reported in October 2007 from the first 13 patients treated in a 30-patient multi-arm Phase I/II single-center clinical trial to evaluate the safety of VRCs and unexpanded bone marrow cells in the treatment of chronic diabetic foot wounds associated with CLI.

A German researcher from the Heart & Diabetes Center located (Bad Oeynhausen, Germany) treated four diabetic patients with ischemia-related chronic tissue ulcers with Aastrom’s VRCs. (In addition, seven patients were treated with normal unexpanded marrow cells, and two patients did not receive cells.)

Twelve months after the treatment, all patients in the interim analysis who were treated with VRCs reported no major amputations, no cell-related adverse events, and healing of all open wounds.

Of the seven patients treated with unexpanded bone marrow cells, five reported results similar to the VRC-treated patients 12 months post-treatment, one reported similar results to the VRC-treated patients 18 months post-treatment, and one patient underwent a major amputation.

Of the two patients who only received wound care (no cells), one patient received a major amputation and one patient experienced no improvement in wound healing after 12 months.

According to Aastrom, patient follow-up is now complete and final data is expected to be reported sometime before the end of June.

Although these patient samples are small, they do offer an early indication of the potential effectiveness of the expanded cells derived from the TRC process.

The big question is: Will Aastrom stay on its feet long enough to enjoy the fruits of any success it achieves with the clinical trial program?

**Finance & Funding Situation**

At the end of December 2008, Aastrom had about $16.5 million in cash, and another $6 million in short-term investments.

During the last half of 2008 the company’s average cash burn rate was about $1.2 million a month.

The burn rate is going to increase in 2009 to about $1.5 million a month, the company says, because expenses related to the IMPACT-DCM trial will increase.

At that rate, the company will come close to depleting its coffers by the fourth quarter of 2009 unless it can generate a cash infusion.

It obviously will not generate cash from product sales, probably for several years.

Other sources of cash this year and in the longer term include some sales of cell products and manufacturing supplies to academic collaborators, grant revenue, and research funding.

Its agreement with Fusion Capital Partners gives it the right to sell common stock to that

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company from time to time. This arrangement will bring in anywhere from $60,000 to $2 million at a time, up to a total of $15 million over 25 months.

**Conclusion**

Beyond that, what possible tactics is Aastrom exploring to keep itself afloat and keep its clinical trials program active?

In addition to suspending two of its four TRC development programs, it has taken other slenderizing actions: cutting staff and trimming overhead expenses.

Aastrom says in its February 2009 10-Q report to the SEC: “We have experienced significant management turnover, and if we cannot attract and retain key personnel, then our business will suffer.”

[NOTE: Only two members of the Aastrom management team have been with the company longer than three years. None of the top executives listed in the May 2006 edition of the Guide to Stem Cell Research Companies is still with Aastrom.]

Downsizing can have negative ripple effects. As a regenerative medicine company Aastrom competes with a lot of other firms in its industry, not to mention academic and private research institutions, for top-notch scientific and management personnel.

Will potential employees want to take a chance on a company that is feeling the economic pinch?

Aside from selling more stock, either privately or publicly, the company’s other strategy for keeping its head above water is through relationships with other regenerative medicine companies.

The company has said that these relationships can take a couple of forms: what the company calls “complementary regenerative medicine business activities.”

One possibility is acquiring another company. A good assumption is that a suitable acquisition would be an entity that would somehow create value for Aastrom. A so-called “synergistic” acquisition would, for example, boost cash flow by either increasing revenues or reducing expenses. A significant consideration is funding of any deal. Would it be through cash (not likely), debt or equity?

Another possibility is collaborations. A regenerative medicine partner could contribute needed resources (cash, staff, lab space, etc.) to expedite research and development and the push to market. In addition, Aastrom could benefit from technology or product licensing fees.

Unfortunately, no company is in complete control of its future. Because of Aastrom’s relatively low level of cash reserves, however, it is especially susceptible to quaking and shaking in the economy and in the regenerative medicine industry. Many risk factors are involved.

For the company to emerge from the development stage, it has to move its high-promise products successfully through clinical trials and win FDA approval for market introduction.

It can’t do this without a sustained cash infusion: “significant additional funding,” as the company says.

“… We do not anticipate generating significant sales in any geographic region until we have sufficient evidence of clinical safety and efficacy to ensure marketplace acceptance and product reimbursement and to justify the investment in manufacturing, sales and marketing infrastructure. However, we are currently generating limited, nominal sales of TRC-based products and expect to continue this level of activity.”

That’s good news, albeit a slim thread on which to hang a company’s hopes.

At any rate, we intend to keep an eye on Aastrom over the coming months. It may soon be nearing its “season in the sun.”
Closer And Closer To Commercialization Of A Stem Cell-Based Therapeutic

[EDITOR'S NOTE: Subsequent to the writing of this article, Osiris announced that it has discontinued its Phase III clinical study of Prochymal as a treatment for Crohn’s disease because of suspected problems with study design. You can read the news article about the study discontinuation, beginning on Page 10.]

Osiris Therapeutics (NASDAQ:OSIR, Columbia, Md.) is another company that is working quietly, diligently, away from the harsh limelight of embryonic stem cell research. It, too, is striving to develop a marketable therapeutic using stem cells harvested from adult bone marrow.

Osiris’ technology is based on the pioneering work of Dr. Arnold Caplan and his colleagues at Case Western Reserve University. They showed that mesenchymal stem cells (MSCs) can engraft and selectively differentiate, based on the tissue environment, to muscle, bone, cartilage, marrow stroma, tendon and fat. Due to their cellular origin and phenotype, these cells do not provoke an immune response, allowing for the development of products derived from unrelated human donors.

Osiris hopes to be the first company to receive U.S. Food and Drug Administration (FDA) marketing approval of a stem cell drug: Prochymal.

Assuming that the company manages to navigate the minefield of risk factors that can sink any small development stage company, it has a good chance of meeting that goal. It has several clinical trials of Prochymal in the works, for several diseases.

The company’s lead biologic drug candidate, Prochymal, is being evaluated in Phase III clinical trials for four indications, including acute and steroid refractory graft versus host disease (GvHD), Crohn's disease and for the repair of gastrointestinal injury resulting from radiation exposure.

It is the only stem cell therapeutic currently granted both Orphan Drug and Fast Track status by the FDA. Prochymal is also being developed for the repair of heart tissue following a heart attack, for protection of pancreatic islet cells in patients with type 1 diabetes, and for the treatment of chronic obstructive pulmonary disease (COPD).

The company also has underdevelopment a drug known as Chondrogen for osteoarthritis in the knee.

In the fourth quarter of 2008, the company inked a collaboration agreement with Genzyme Corporation for the development and commercialization of Prochymal and Chondrogen.

Osiris retained the rights to commercialize Prochymal and Chondrogen in the United States and Canada, while Genzyme has exclusive rights to commercialize Prochymal and Chondrogen in all other countries (except with respect to GvHD in Japan, where Prochymal has previously been licensed to another).

The company has also partnered with Genzyme to develop Prochymal as a medical countermeasure to nuclear terrorism and other radiological emergencies.

A January 2008 contract from the U.S. Department of Defense calls for development and stockpiling of 10,000 doses of Prochymal for the repair of gastrointestinal injury resulting from acute radiation exposure.

Under an agreement with the Juvenile Diabetes Research Foundation, Prochymal is being developed as a treatment for the preservation of insulin production in patients with newly diagnosed type 1 diabetes mellitus.

Mesenchymal Stem Cells

Osiris’ two drug candidates (Prochymal and Chondrogen) use human mesenchymal stem cells (MSCs), which have anti-inflammatory properties
and can prevent fibrosis or scarring, giving MSCs the potential to treat a wide variety of medical conditions.

The company believes Prochymal and Chondrogen have advantages over other stem cell therapeutics in development because:

– The cells come from adult bone marrow, a readily available source. They are drawn from the hips of volunteer donors between the ages of 18 and 30 years, using a simple needle and syringe aspiration. “Because the cells are obtained from consenting adult donors, we are able to largely avoid the ethical controversy surrounding embryonic and fetal stem cell research.”

– Using its proprietary manufacturing methods, the company can grow MSCs in a controlled fashion to produce up to 10,000 treatments of its drugs from one bone marrow donation. “Our ability to produce a large quantity of treatments from one donation provides us with manufacturing efficiencies and product consistency that are essential to commercialization.”

– Based on its clinical experience, the company believes its drugs are not rejected by the patient's immune system and do not require matching. “This universal compatibility allows us to produce a standardized product available to all patients in almost any medical setting.”

– The drugs can be stored frozen at end-user medical facilities until they are needed. The company believes medical facilities will be able to prescribe and dispense the products in much the same way as conventional drugs. “In contrast, other stem cell technologies under development require weeks to prepare after a patient's need is identified.”

Prochymal

Prochymal is being tested to treat medical conditions in a variety of indications. (See chart below.) The drug is being evaluated in Phase III clinical trials for three indications, including first line and steroid refractory acute graft versus host disease (GvHD) and Crohn's disease, and is the only stem cell therapeutic currently designated by the FDA as both an Orphan Drug and Fast Track product. Prochymal is also being developed for the repair of heart tissue following a heart attack.

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(Source: Osiris Therapeutics)
and for the protection of pancreatic islet cells in patients with type 1 diabetes, for the treatment of chronic obstructive pulmonary disease (COPD) and for the repair of gastrointestinal injury resulting from radiation exposure.

**Chondrogen**

The meniscus is a crescent-shaped cushion in the knee joint that protects cartilage and enables the knee to move smoothly. Injury and tears to the meniscus are common and can be traumatic, arising from sports injury, for example, or from degeneration from daily wear and tear. An injured or torn meniscus is painful and typically requires surgical intervention.

The current standard of care for significant injuries is partial meniscectomy surgery, in which the damaged portion of the meniscus is permanently removed.

According to Osiris, there are no FDA approved products available to regenerate meniscal tissue. In several preclinical studies, Chondrogen, a preparation of adult stem cells formulated for direct injection into the knee, regenerated meniscus and prevented osteoarthritis in animal models. At the end of the first quarter of 2006 the company completed enrollment in a Phase I/II clinical trial for Chondrogen, designed to evaluate the safety and preliminary efficacy in patients following surgery to remove torn meniscus.

At the end of the first quarter of 2006, the company completed a randomized double-blind, placebo-controlled Phase I/II clinical trial evaluating Chondrogen for safety and preliminary efficacy based upon regeneration of meniscus at six-months. In November 2007, one-year data for the Phase I/II Chondrogen trial showed improvements in joint condition that correlated with a clinically and statistically significant improvement in pain in patients with osteoarthritis (OA) who received Chondrogen as compared to those treated with the control, hyaluronic acid (HA).

**Risks**

Osiris shares a whole array of risks with other development stage biotech companies. Risks are those negative or undesirable events or conditions that might prevent a company from reaching its strategic goals.

Generally shared risks include potential: inclement financial and funding weather, adverse effects of stock market volatility on share prices, inability to attract and keep top management and scientific talent, failure of clinical trials to prove product safety or efficacy, delays in winning FDA approval of further clinical trials or products, adverse marketing conditions for new products (e.g., will doctors accept novel over traditional therapeutics?), inability to supply enough product to meet market demand, failure of collaborative companies to follow through on product development or marketing plans, lawsuits for product liability or intellectual property issues, etc.

Every public company is aware of these shadowy monsters hiding in the closet. And every company shares its thoughts on them with potential investors in their SEC filings.

One risk factor that could prove especially troublesome for stem cell research companies is the possibility that a newly developed, newly FDA-approved product might have to be priced so high that insurance companies will refuse to reimburse patients for the costs. Insurance companies might also decide that a new product is too experimental, unnecessary, or inappropriate, and deny reimbursement.

If this happens, the ability of a smaller company with shallow pockets to get its product accepted in the marketplace would diminish significantly. Osiris has an accumulated deficit of $275 million since its founding. Whether that amount would be taken into consideration in the establishment of pricing for its products is an open question. But it’s a question that current and future investors must have in the back of their minds.

Osiris is also concerned about the fact that the regulation of a new product continues after FDA approval and compliance with regulation is expensive.

“It is likely that Prochymal, if approved for GvHD (Graft versus Host Disease) based on (Continued on page 9)
our currently contemplated Phase III trial, will receive conditional approval by the FDA, and we will be required to conduct Phase IV clinical trials to obtain full approval,” the company said in its most recent SEC 10-K report. “Even if we obtain full approval of a product, that approval is subject to limitations on the indicated uses for which we can market it.”

Management Stock Ownership

It is a well-known tenet of company evaluation that management should own a very large interest, anywhere from 50 percent to 70 percent of the stock. Significant management ownership usually means management will do everything within reason to get and keep the stock up. In the case of Osiris, about half of the stock is owned by executive officers, directors and beneficial owners who have at least a five percent stake. One would expect that this group would have a big say in matters, including the naming of directors, approving mergers and acquisitions, and other major corporate business. One would also expect that their decisions would be based on whether stock value would be affected positively or negatively.

Osiris, however, has another wrinkle that somewhat obscures the investment picture. Board Chairman Peter Friedli and his company Friedli Corporate Finance, Inc., own about 43 percent of Osiris common stock. Not unexpectedly, Friedli has a big say in any corporate decisions that require stockholder approval. Friedli’s interests in any decisions may or may not coincide with the interests of other stockholders, inside or outside the company.

It should be noted that none of the current executive officers has been with the company longer than five years.

Company Revenue

Most of the $10 million in revenue Osiris received in 2008 came from research agreements, government contracts, and royalties. The company sold its Osteocel business in 2008 in a deal worth potentially $85 million. (The company has received about $35 million of that already.) Other potential non-product-related revenues include the development and commercialization collaborative agreement with Genzyme (for Prochymal and Chondrogen) worth about $1.4 billion. The company used the first $75 million from that deal to retire debt. Another $55 million will be paid to Osiris in July of this year. (The company is amortizing the revenue over the next three years, as agreed-upon milestones are reached.) The company’s Defense Department contract (10,000 doses of Prochymal for acute radiation syndrome) is worth $225 million. The company also signed a collaborative agreement with the Juvenile Diabetes Research Foundation (JDRF) under which JDRF provides $4 million to support development of Prochymal as a treatment for newly diagnosed Type 1 diabetes patients. The second $2 million payment from this agreement will be made this year.

Competition

If approved, Prochymal will likely be the first drug indicated for the treatment of acute GvHD. The competitive landscape in Crohn's disease is more crowded, however, and if approved for this indication, Prochymal will compete with Johnson & Johnson's Remicade, Abbott's HUMIRA, Biogen's Tysabri and UCB's Cimzia.

If approved, Chondrogen will compete with pain relievers such as acetaminophen, non-steroidal anti-inflammatory drugs, intra-articular injection of corticosteroid or hyaluronic acid.

However, none of these have proven disease-modification ability, one of the goals of Chondrogen development.

Competition in the future may come from other companies researching and developing stem cell therapies. These could include Aastrom Biosciences, Advanced Cell Technology, Athersys, Cellerant Therapeutics, Cognate Therapeutics, Cytori Therapeutics, Gamida Cell, Geron, Mesoblast, MultiCell Technologies, Neuronyx, Theradigm, ViaCell and StemCells.

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Conclusion

Though Osiris has consistently lost money ($275 million) since its inception, it has managed to stay afloat, thanks to timely investments by venture capitalist Peter Friedli (and his companies), as well as the collaborative deals with Genzyme and the Juvenile Diabetes Research Foundation, sale of its Osteocel bone regeneration product to NuVasive, Inc., and the contract from the U.S. Dept. of Defense.

Due to its experience with the Osteocel bone regeneration product and other current pipeline product candidates, the company seems to have the necessary clinical, regulatory, manufacturing, and commercial capabilities to successfully bring its drug candidates to market.

Its cash position is comfortable at $62 million. It has almost no debt. Its current liabilities comprise accounts payable and deferred revenue. The current ratio is 2.21, which is excellent.

The company’s clinical trials are moving along smoothly. A year ago, the company said that of the three indications that are in the final phases of testing (two forms of GvHD, and Crohn’s disease), it expects Prochymal to reach the GvHD market first. Assuming marketing approval, the company plans to develop a small, specialized sales force and marketing organization to promote Prochymal. A smaller sales force would be required because of the small number of bone marrow transplantation hospitals treating patients with GvHD in the United States and Canada and the lack of effective treatments for this population.

Although Prochymal for GvHD is the most likely to win the commercialization derby, at a projected market value of $240 million it is not the biggest of the potential markets, the company said. That distinction goes to the chronic obstructive pulmonary disease (COPD) market, which the company projects to be in the $5 billion range. Results from clinical testing of Prochymal for COPD are, however, a long way away.

All in all, Osiris seems well-positioned to bring a product to market within the next couple of years. It is definitely worth watching closely. Pay special attention to news about Prochymal as a treatment for GvHD.

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Stem Cell Company News Highlights

Trial Design Problems Force Osiris To Discontinue Enrollment In Crohn’s Clinical Trial

Columbia, Md.-based Osiris Therapeutics, Inc. (OSIR) said on March 27 that it has elected to end enrollment at 210 patients in its Phase III trial evaluating Prochymal for Crohn’s disease.

The company had planned to enroll 270 patients.

The announcement bashed the company’s shares in early trading on March 27, pushing the price down by 25 percent.

The company said it believes a design flaw in the trial resulted in significantly higher than expected placebo response rates.

“The decision was made after the trial’s final scheduled interim analysis showed that one of the two Prochymal dose arms had crossed a futility boundary,” the company said. “The dose arm was unlikely to achieve the primary endpoint of remission because of the high placebo response rate. This latest analysis continued to show no serious safety concerns with the therapy and safety was not a factor in the decision to stop enrollment.”

“We had a situation where we were experiencing much higher than expected placebo

Investor Tip: Insider Selling

Compared to insider buying of company stock, insider selling of stock is not as reliable an indicator. The main reason is that a company officer may have a hundred personal reasons for selling shares. Just remember to watch the trends. If the person has been only selling shares over a period of time, it may be an early signal of a serious problem somewhere in the company down the line (perhaps many months away).
response rates,” said CEO C. Randal Mills. “As we looked into possible causes, we discovered what we believe to be a systemic design flaw in the trial that would likely affect the utility of the data for purposes of registration. After careful discussion with the FDA, we elected to discontinue enrollment rather than attempt to re-power the trial. We will keep the trial blinded and expect a solid data package for use in designing future trials in Crohn’s disease and to bolster Prochymal’s safety database.”

The Prochymal Crohn’s program consists of two separate but related double blinded trials. The first trial evaluates patients’ initial response to two dose levels of Prochymal as compared to placebo.

The potential trial design flaw may be related to the fact that patients responding to the initial therapy were eligible to participate in a second, longer-term trial evaluating Prochymal as a maintenance therapy.

Because the current standard for determining response of Crohn’s patients to therapy is largely subjective, there may have been response bias to meet the eligibility requirements for continuation of therapy in the longer-term maintenance trial.

“We fully agree with the decision by Osiris to end enrollment in this trial due to what appears to be a problem with the trial design,” said David Meeker, M.D., executive vice president at Genzyme Corporation. “We think this is prudent and will enable a more efficient path forward. The data from this trial will be extremely valuable in designing the subsequent trial and enabling the continued development of this first-in-class therapy.”

Webcast and Conference Call

Osiris Therapeutics’s pipeline of internally developed biologic drug candidates under evaluation includes Prochymal for inflammatory, autoimmune, and cardiovascular indications, as well as Chondrogen for arthritis in the knee.

Contact: http://www.Osiris.com

Bone Marrow Stem Cell Injections Show Promise To Treat Spinal Cord Injury

Quality Of Life Also Improves Significantly

Injecting a patient’s own bone marrow-derived stem cells directly into the spinal column using multiple routes can be an effective treatment for spinal cord injury (SCI) that returns some quality of life for SCI patients without serious adverse events, according to a new clinical study.

Researchers from DaVinci Biosciences (Costa Mesa, Calif.), in collaboration with Hospital Luis Vernaza in Ecuador, reported on eight patients with SCI (four acute and four chronic) to whom they administered autologous (patient’s own) BMCs directly into the spinal column, spinal canal and intravenously for each patient and followed for two years using MRI imaging to assess morphological changes in the MRI.

“Our objective in this study was to demonstrate that multiple route administration of BMCs for SCI is safe and feasible,” said corresponding author Dr. Francisco Silva. “To date, we have administered BMCs into 52 patients with SCI and have had no tumor formations, no cases of infection or increased pain, and few instances of minor adverse events. We also found that patient quality of life improved.”

In addition, Dr. Silva told us, the treatments offer benefits greater than just improvements in quality of life.

“The treatment may repair the damaged spinal cord as seen through the MRI (magnetic resonance imaging) and the physical manifestations following the administration of stem cells,” he said. “The MRI clearly demonstrates morphological changes occurring within the spinal cord.”

There is no cure or effective treatment for spinal cord injury, a disorder affecting millions globally.

Tissue loss from the primary injury and the complexity of cell Types required for functional recovery lead the list of considerations.

Once more, to be considered successful,

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any treatment should ultimately help to improve patient quality of life and demonstrate functional improvements.

“Autologous stem cell transplantation of BMCs can promote the growth of blood vessels and, therefore, represent an alternative therapy,” Silva said.

Following primary trauma to the adult spinal cord there is evidence of hemorrhage and blood flow is attenuated, he said.

The disruption of blood flow leads to spinal cord infarction, the disruption of the blood-spinal cord injury barrier, swelling and the release of molecules influencing spinal cord perfusion and ischemia, a restriction in blood supply.

The eight patients treated with BMC transplant in the study were followed for two years. They included four in early or acute stage (5 days to 7 months post injury) and four in longer term or chronic stage (5 to 21 years post injury), according to Dr. Silva.

All of the patients were paraplegic, and had suffered different types of injuries, including a gunshot wound.

Dr. Silva said the administration of stem cells improved the patients’ mobility, sensation, and bladder function leading to substantial improvement in quality of life.

Quality of life issues that pertained to the Barthel index also improved (i.e., bathing, grooming, dressing, transfer, mobility, bowel, bladder, etc.).

“BMCs are well known for their ability to grow blood vessels,” Dr. Silva said. “This angiogenesis is necessary for wound healing and establishing a growth permissive environment. We hypothesized that improved blood flow and oxygen supply could contribute to functional improvements for SCI transplanted with autologous BMCs.”

The patient with the gunshot wound marked the first time a spinal gunshot victim had received BMC transplants through multiple routes.

“It is important to note,” Silva said, “that all of our patients with acute injuries improved significantly with no signs of deterioration or impediment of presumed spontaneous recovery.”

According to Dr. Svitlana Garbuzova-Davis, a spinal cord researcher at the University of South Florida, the study highlights the value of using several different simultaneous routes for the administration of stem cells, as well as the benefit of the cells themselves.

“While it would be interesting to know the respective contribution of each route of administration, this study does appear to support the need to move to carry out double blind clinical trials of BMCs in SCI, especially if a non-invasive route could be used.”

The study was in *Cell Transplantation* (Vol. 17 No.12).

Contact: Dr. Francisco Silva, 949-515-2828, fsilva@dvbiosciences.com

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**Basic Research**

**Company’s SC Technology Demonstrates Efficacy In Parkinson’s Animal Model**

Human-derived adult stem cells may be induced to differentiate in vitro into neural-like cells and, once injected into the brain, improve impaired motor behavior in an experimental model of Parkinson’s disease, according to a new study.

Research, by scientists working with **BrainStorm Cell Therapeutics Inc.** (BCLI, Petach Tikvah, Israel) is the second recent peer-reviewed publication demonstrating the potential promise of BrainStorm’s technology, which induces human adult stem cells to become cells that release neurotrophic factors (NTF cells).

A publication last month by the same scientific team documented that engrafted human NTF cells survived and expressed neuronal markers after 120 days and acted to regenerate the damaged dopaminergic nerve system in the same rodent model of Parkinson’s disease.

The findings resulted from experiments (Continued on page 13)
conducted by Dr. Daniel Offen in collaboration with colleagues at BrainStorm and at the Tel-Aviv University.

They demonstrate that cells processed using BrainStorm’s technology produce and secrete significant amounts of essential factors for brain cell function, including glial cell line-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF).

Moreover, the cells transplanted into the standard rodent model of Parkinson’s disease, reduced the motor dysfunction by 50 percent, inhibited the induced dopamine depletion and restored the dopaminergic cell’s terminals.

In lay terms, all of those findings are consistent with attenuating the tremor and other motor symptoms associated with Parkinson’s disease.

In addition to the marked improvement in symptoms, the study also demonstrated via magnetic resonance imaging (MRI) and subsequent histological assessment that the transplanted cells migrated toward the experimentally-induced lesion, indicating both their survival and integration into brain tissue.

“On the basis of our findings, we suggest that autologous transplantation of NTF cells, originally derived from a patient’s own bone marrow, may become a novel and potent treatment for Parkinson’s disease and other neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS),” said Prof. Eldad Melamed, professor of neurology at the Tel Aviv University and BrainStorm’s chief medical advisor.

The use of adult stem cells avoids recently demonstrated concerns of tumor growth in association with fetal stem cell implantation, as well as the attendant ethical issues.

Moreover, the use of the patient’s own cells for the NTF cell therapy avoids the potential for graft rejection and the need for long-term administration of immunosuppressive anti-rejection agents.

“Pharmaceutical approaches to treating Parkinson’s, ALS, and other neurodegenerative diseases have largely failed, as evidenced by the dearth of clinical candidates in pharma pipelines,” said Prof. Jonathan Javitt of Johns Hopkins University. “Until the advent of patient-derived stem cell therapy, the safety risks associated with stem cell therapy were considered a major barrier to human therapy. The fact that human cells can be modified into therapeutically valuable cells and survive even when transplanted into an animal model suggests that those same cells may be even more valuable and viable when injected into the patient from whom they were derived.”

The study appears in the online edition of Stem Cells and Development.

BrainStorm Cell Therapeutics is developing adult stem cell therapeutic products derived from autologous (self) bone marrow cells, for the treatment of neurodegenerative diseases.

Contact: http://www.brainstorm-cell.com

Researchers Analyze Mechanism That Enables Adult Cell Pluripotency

Agilent Technologies Inc. on March 5 announced that a research collaboration with the Shanghai (PRC) Institutes for Biological Sciences and Tongji University has achieved new insight into how adult cells can be induced to act like embryonic stem cells (ESC), with the ability to form any type of tissue known as “pluripotency.”

“The value of finding alternatives to embryonic stem cells would obviously be tremendous, and the ability to induce pluripotency in adult cells, discovered in 2006, is considered a breakthrough,” said Jian Li of Agilent Technologies Shanghai, one of the article’s coauthors.

“Now we’re gaining new understanding into how this pluripotency was actually induced.”

The researchers observed a developmental signaling network of 16 signaling pathways, in-

Investor Tip: Venture Stocks

If you’re thinking of investing in penny stocks or stocks with very low share prices, use only a small portion of your investment assets, say 10%-15%, to speculate. Venture stocks are highly volatile. Don’t endanger your liquidity on dizzying roller coaster rides.
cluding nine that had not previously been as-signed roles in maintaining or inducing pluripo-tency.

The study used Agilent chromatin immunoprecipitation-on-chip (ChIP-on-chip) and gene expression microarrays to study molecules known as “Yamanaka factors” and their roles in inducing pluripotency in mouse cells.

Agilent provided the microarray kits for this research under an Agilent grant issued in 2008.

Microarrays are glass wafers containing large numbers of DNA probes used to analyze genomic activity. ChIP-on-chip microarrays are used to observe activity at “promoter regions” on the genome, where chemical events activate and deactivate various genes to control cellular functioning.

Their findings were published in the journal Cell Research (“Yamanaka factors critically regulate the developmental signaling network in mouse embryonic stem cells,” Cell Research, 2008 18:1177-1189).

Contact: http://www.agilent.com

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Drug Activates Stem Cells To Improve Cardiac Function After Heart Attack

San Diego, Calif.-based Cardium Therapeutics (NYSE Amex: CXM) on March 27 reported on an NIH-funded, pre-clinical study showing that mesenchymal stem cells (MSCs) can be activated using Ad5IGF-1 into the cells while they are being processed outside of the body or ex vivo.

Mesenchymal stem cells are multipotent cells that develop into bone and cartilage tissue.

Corgentin (Ad5IGF-I) is a DNA-based therapeutic using the insulin-like growth factor-I gene carried by an adenovector.

The product is being designed as a one-time treatment to promote the repair and restora-tion of damaged cardiomyocytes.

Upon reintroduction into the body, Ad5IGF-1 activated stem cells substantially reduced heart attack related tissue damage (infarct size), caused extensive angiomyogenesis, and improved left ventricular ejection fraction and fractional shortening.

MSCs not treated with Ad5IGF-1 had significantly less therapeutic effect in this preclinical model of heart attack.

The authors concluded that the observed synergy between MSCs and Ad5IGF-1 in myocardial regeneration after a heart attack may be due to IGF-1-induced release of various cytokines and chemokines, including SDF-1 alpha, contributing to massive stem cell mobilization from the bone marrow and their increased homing in the injured heart muscle.

The research was conducted by scientists at the University of Cincinnati.

“Recent findings indicate that mesenchy-mal stem cells, which are processed ex vivo before reintroduction into the body, tend to lose certain capabilities required for effective binding and retention within injured heart tissue such as that occurring after a heart attack,” said chief scientific officer Gabor M. Rubanyi, M.D., Ph.D.

The company believes that the effectiveness of the stem cells can be substantially improved through a targeting mechanism that involves the binding of the CXC chemokine receptor 4 (found on these stem cells in the bone mar-row but reduced after ex vivo expansion) with the stromal-derived factor-1 alpha ligand that is expressed in ischemic heart tissue following a heart attack.

This suggests that treatment of mesenchy-mal stem cells ex vivo with an Ad5IGF-1 bio-logic, such as Cardium’s Corgentin product can-didate, will lead to local production of insulin-like growth factor-1 protein to enhance this process and amplify the delivery and retention of stem cells within injured heart tissue.

The company said the recently-published research findings from the University of Cincin-nati provide independent support of this possible mechanism of action and underscore the potential use of Cardium’s Corgentin candidate in stem cell therapies aimed at the treatment of heart attack and other indications."

(Continued on page 15)
“Cardium has been developing a portfolio of innovative DNA-based growth factor therapeutics for cardiovascular and related applications. Our Corgentin (Ad5IGF-1) product candidate is designed to lessen tissue injury and promote myocardial repair and restoration following a heart attack,” said CEO Christopher J. Reinhard.

Cardium Therapeutics, Inc., and its subsidiaries are focused on the development, manufacture and sale of innovative therapeutic products and devices for cardiovascular, ischemic and related indications.

The article (“IGF-1–Overexpressing Mesenchymal Stem Cells Accelerate Bone Marrow Stem Cell Mobilization via Paracrine Activation of SDF-1 alpha/CXCR4 to Promote Myocardial Repair”) was published in Circulation Research (Circ Res. 2008; 103(11): 1300-1308).

Contact: http://www.cardiumthx.com

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**Finance & Funding**

**Company To Use $5 Million Loan To Develop Treatments For Eye Diseases**

Worcester, Mass.-based Advanced Cell Technology, Inc. (PINKSHEETS: ACTC) said on March 11 that it has borrowed $5 million from an unnamed life sciences fund to develop the company's retinal pigment epithelium (RPE) cells program for the treatment of diseases of the eye.

The investor, according to the company, is an affiliate of a large shareholder in Advanced Cell.

Cash will be drawn from the loan in exchange for issuance of Series A-1 Convertible Preferred Stock.

The company said it believes the proceeds will be sufficient for the company to file an IND for its RPE program this summer, and will allow the company to complete both Phase I and Phase II studies in humans.

An IND approved by the Food and Drug Administration is required to begin clinical trials in the United States.

The company may draw down funds from the loan as needed for clinical development of the RPE Program.

The company said the preferred stock pays dividends, in kind of preferred stock, at an annual rate of 10 percent, matures in four years from the draw down date, and is convertible into common stock at 75¢ per share. The company also paid the Investor a commitment fee equal to five percent of the loan facility.

“Diseases of the eye affect more than 30 million people worldwide and represents a $28 billion market,” said CEO William Caldwell. “We believe that this funding will allow us to advance our proprietary technology, which has the potential to generate stable cell lines, through key stages of clinical development, generating significant value for shareholders.”

The company earlier in the month said it had received $400,000 in additional funding from a final payment from CHA Biotech Co, Ltd., a Korean-based biotechnology company and research grants from the National Institutes of Health.

The company said proceeds will be used to support the company’s retinal pigment epithelium cells (RPE) program.

The company anticipates filing an IND with the FDA during the second half of this year.

Contact: http://www.advancedcell.com

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**Investor Tip: Venture Stocks**

If you’re thinking of investing in penny stocks or stocks with very low share prices, use only a small portion of your investment assets, say 10%-15%, to speculate. Venture stocks are highly volatile. Don’t endanger your liquidity on dizzying roller coaster rides.
Snapshot of Select Public Stem Cell Companies

<table>
<thead>
<tr>
<th>Company</th>
<th>Date</th>
<th>Closing price</th>
<th>52-week high</th>
<th>52-week low</th>
<th>Current Ratio (1)</th>
<th>Cash</th>
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<tbody>
<tr>
<td>Stem Cell Technology International (SCII, OTC BB)</td>
<td>3/20/09</td>
<td>.075</td>
<td>.24</td>
<td>.00</td>
<td>.46</td>
<td>0 (2)</td>
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<tr>
<td>Bio Matrix Scientific Group Inc. (BMSN, OTC BB)</td>
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<td>.15</td>
<td>1.39</td>
<td>$10,000 (09/08)</td>
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<td>Athersys (NASDAQ:ATHX)</td>
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<td>4.23</td>
<td>.15</td>
<td>12.58</td>
<td>$31,600,000</td>
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<td>Medistem Laboratories (MEDS.PK, OTC, Pink Sheets)</td>
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<td>6.50</td>
<td>.11</td>
<td>5.83</td>
<td>$694,000 (9/08)</td>
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<td>.30</td>
<td>.02</td>
<td>.01</td>
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<tr>
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<td>.15</td>
<td>11.46</td>
<td>$16,492,000 (06/08)</td>
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<tr>
<td>Osiris Therapeutics (NASDAQ:OSIR)</td>
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<td>21.65</td>
<td>10.80</td>
<td>2.21</td>
<td>$61,298,000</td>
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</tbody>
</table>

(1) Ratio of current assets to current liabilities. Red number indicates worrisome cash and/or debt situation.
(2) Company is operating with negative working capital.

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