Researchers from the University of Pittsburgh (PA, USA) are investigating whether fat-derived stem cells might provide a new and improved method of breast reconstruction following surgery.

Potential for use of stem cells in breast resconstructive surgery

Breast cancer is the most common cancer experienced by women worldwide. The American Cancer Society estimates that over 214,000 new cases of breast cancer will be diagnosed in 2006 and data from the American Society of Plastic Surgeons show that more than 80,000 breast reconstruction surgeries are performed every year.

The discomfort and psychosocial stresses caused by mastectomy of one or both breasts should not be ignored. Current surgical options for breast reconstruction are quite invasive and involve either implants or transplantation and reshaping of fat from another part of the body. Adipose- or fat-derived stem cells may be able to provide a better, alternative source of durable replacement soft tissue.

'Adipose- or fat-derived stem cells may be able to provide a better, alternative source of durable replacement soft tissue.'

Stem cells have been heralded by many as a potential cure for a wide variety of diseases, ranging from the neurological, such as Parkinson's disease, to autoimmune disorders, such as diabetes. Their potential for use in tissue diseases also originates from their ability to develop into specific cell types. Fat-derived stem cells have demonstrated, when subject to differing laboratory conditions, differentiation into cells characteristic of bone, cartilage, fat, nerve, muscle and blood vessels.

Teams from the Universities of California in Los Angeles (CA, USA) and the University of Pittsburgh first reported the isolation of stem cells from fat in 2001. This has led to research investigating their potential with regards to the treatment of heart attack, stroke or bone injury, among others.

It is estimated that removal of 1 lb of fat in a procedure such as a tummy tuck can yield up to 200 million stem cells. When cultured in a laboratory, these can be multiplied up to ten times over a 2-week period. Therefore, it is hoped that surgeons will be able to obtain the required stem cells from a patient's stores of abdominal fat.

The current focus at the University of Pittsburgh involves a combination of fat-derived stem cells with an extracellular matrix of microscopic beads that has regenerative properties.

Results from preliminary animal studies are promising. The stem cells appear to attach to the beads easily and can be induced into differentiating into mature fat cells. When injected subcutaneously into rats, the cellular combination formed what the researchers describe as 'a mound' of tissue.

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Fat from breast cancer patients is currently being used as the stem cell source in order to ascertain if these behave in the same way as those derived from healthy women. In addition, studies are also being conducted into whether or not these stem cells have any impact on cancer cells. "A major question is whether or not they will in some way promote the growth of cancer cells. We certainly hope this will not be the case," commented J Peter Rubin, leader of the research group and Assistant Professor of Plastic and Reconstructive Surgery at the University of Pittsburgh.

If successful, this method has the potential for regenerating new breast tissue, a goal that will certainly be appreciated by the many women who are affected by breast cancer and mastectomy every year. In fact, according to the American Cancer Society, over 214,000 new cases of invasive breast cancer will be diagnosed by the end of this year.

Heart attack patients to receive therapy with their own stem cells

A total of 50 patients across two hospitals in London (UK) are due to have stem cells removed from their own bone marrow and injected into their heart as part of a groundbreaking new attempt to repair the damage caused to the heart tissue as a result of heart attack.

It is hoped that the stem cells will develop into healthy heart tissue and repair the damage caused by acute heart attack, in order to delay or prevent the progression to heart failure. The trial, which is to receive funding from the UK Stem Cell Foundation, will take place at the London Chest Hospital and Heart Hospital and will be the first to examine the effects of using stem cells within the 5-h time window following an acute heart attack.

The project follows on from previous studies in Europe that showed success in animal models. Speaking of the project, Dr Anthony Mathur, Consultant Cardiologist at the London Chest hospital, commented "If we can demonstrate improvement in the quality of life of patients, then this will be a significant step forward in the treatment of heart disease." He added that "because the stem cells are taken from the patient themselves, there are minimal ethical issues surrounding this procedure. There is also less likelihood of rejection complications."

Priority Paper Alerts

A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain.

Wernicke JF, Pritchett YL, D'Souza DN *et al*. *Neurology* 67(8), 1411–1420 (2006).

This randomized, double-blind, controlled trial aimed to evaluate the efficacy of the serotonin and norepinepherine reuptake inhibitor, duloxetine, in the reduction of pain and secondary outcome measures in a group of patients with diabetic peripheral neuropathic pain (DPNP). Administration of duloxetine 60 mg (once and twice daily) provided an improvement in the management of DPNP with a rapid onset of action. The trial further confirms previous findings that the drug is effective and safe for the management of DPNP at doses of 60 mg once and twice daily.

Evidenced-based treatment of opioid-dependent patients.

Van den Brink W, Haasen C. *Can. J. Psych.* 51(10), 635–646 (2006).

By a process of screening of all available published studies on the treatment of opioid dependence, this trial concluded that opioid dependence is a chronic, relapsing disorder that is difficult to cure. However, effective treatments are currently available to stabilize patients, which results in an increase in life expectancy and quality of life.

Epirubicin and cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy for early breast cancer.

Poole CJ, Earl HM, Hiller L, Dunn JA, Bathers S, Grieve RJ, Spooner DA, Agrawal RK, Fernando IN, Brunt AM, O'Reilly SM, Crawford SM, Rea DW, Simmonds P, Mansi JL, Stanley A, Harvey P, McAdam K, Foster L, Leonard RC, Twelves CJ; NEAT Investigators and the SCTBG. *N. Engl. J. Med.* 355(18), 1851–1862 (2006).

Describes two trials, the National Epirubicin Adjuvant Trial (NEAT) and the BR9601 trial, which examined the efficacy of anthracyclines in the adjuvant treatment of early breast cancer in 2391 women with early breast cancer.NEAT compared four cycles of epirubicin, followed by four cycles of CMF, with six cycles of CMF alone. The BR9601 trial examined four cycles of epirubicin, followed by four cycles of CMF, with eight cycles of CMF alone every 3 weeks. Comparison of the trials concluded that epirubicin plus CMF is more effective than CMF alone as adjuvant treatment for early breast cancer.

Artificial pancreas to control insulin levels in young patients with Type 1 diabetes

A team of scientists from the University of Cambridge (Cambridge, UK) have begun work on the development of an artificial pancreas for use in children and adolescents with Type 1 diabetes. It is hoped that the 'closed-loop' device, composing a glucose sensor with an insulin pump, will be able to regulate the highly variable blood glucose levels observed in children and adolescents, by measuring glucose levels on a 'minute-to-minute' basis and calculating the correct dose of insulin to be delivered by the pump. Clinical trials of the device are due to begin in January 2007.

Lead researcher with the group, Roman Hovorka, explained "Insulin needs to be more accurately released to attain near-normal levels of blood glucose and to reduce the risk of dangerous low blood glucose levels – the greatest fear for parents of people with diabetes as it can result in hospitalization, coma and rarely, permanent brain damage or death, if not treated in a timely manner."

He continued that the use of an artificial pancreas would "enable the juveniles to maintain healthier, more stable blood sugar levels."

It is hoped that the trials will provide those involved with the ability to monitor their blood glucose at home using the device after 2 years, and to provide commercial availability within the next 4–7 years.

It is estimated by the American Diabetes Association that one in three people born in the USA after the year 2000 will develop diabetes in their lifetime. In addition, Type 1 diabetes is now one of the most common diseases of childhood, more so than cancer, multiple sclerosis and cystic fibrosis, and can reduce life expectancy by up to 15 years.

HIV gene therapy shows promise as alternative to antiretroviral drugs

The many complications and side-effects, in addition to the mounting resistance to antiretroviral drugs, have highlighted the importance of the development of an alternative to therapy for the millions of HIV sufferers worldwide. It is for this reason that the results from a recent trial of five patients treated at the University of Pennsylvania (PA, USA) with HIV gene therapy, have been greeted with optimism and hope.

Researchers have treated patients who had previously not responded to antiretroviral therapy with a disabled form of the HIV virus carrying added genetic material to block reproduction. Treatment over the 9-month period resulted in the stabilization and, in one case, sustained, dramatic decrease, in viral load, suggesting a future for the use of gene therapy in place of antiretroviral drugs.

The results of the trial have been met with caution, however, as the trial was not large enough nor sufficient to measure long-term side effects, with Bruce Levin, Researcher with the group, commenting "Just because this has produced encouraging results in one or two patients doesn't mean it will work for everyone. We have much more work to do."

Risk of development of chronic fatigue syndrome linked to early childhood trauma

According to results from two studies, published in the November issue of the *Archives of General Psychiatry*, trauma experienced during childhood, in addition to emotional instability at any point in life, may potentially be risk factors for the development of chronic fatigue syndrome (CFS).

There are an estimated 1 million diagnosed cases of CFS in the USA, with millions more suffering from conditions similar to the disease but not reaching the strict requirements for diagnosis. CFS is observed more frequently in women between the ages of 10 and 59 years and is estimated to cost the US economy US$9 billion annually.

"We're talking about the biological underpinnings of a real and very debilitating illness."

Speaking independently of the study results, Nancy Klimas of the University of Miami Miller School of Medicine (FL, USA), commented: "We're not talking about a bunch of stressed-out people. We're talking about the biological underpinnings of a real and very debilitating illness." She added that the purpose of studies such as these is to "remove the stigma of a psychiatric overlay and put it back in biology, where it belongs."

Participants in one of the studies were asked to complete a questionnaire on childhood trauma (sexual, physical emotional, emotional neglect and physical neglect) and psychiatric symptoms, such as depression and anxiety, in addition to medical testing.

However, the results have been met with a note of caution as they are merely preliminary, with Charles Goodstein of the New York University School of Medicine commenting that "These studies bear out what we have learned in medicine and in psychiatry: illnesses of all types are determined in large part by an interplay of genetically determined predispositions and environmental factors." However, he added that "These are interesting elementary papers."

"Illnesses of all types are determined in large part by an interplay of genetically determined predispositions and environmental factors."

Dr Goodstein also commented on the difficulty in diagnosing the disease "CFS remains an elusive condition...it seriously incapacitates patients, but physicians are stumped by the lack of objective signs on physical examination."

In addition to the results from these studies, the US CDC recently launched an awareness campaign for the disease, which still suffers from the stigma previously associated with it. The relative difficulty in diagnosing the disease has in the past led to claims of hypochondriasis and was even dubbed as 'yuppie flu' when it was first recognized in the late 1980s.

The CDC and NIH have also recently announced plans for a US$4 million research program that aims to study the causes of CFS, as well as potential treatment options. The CDC have estimated that as many as 80% of people with CFS may not be aware that they are suffering from the disease as the symptoms, including headache, sore throat and muscle pain, are so common in the general population. Susan Levine, a CFS specialist, added that "This physical disease is quite serious and causes profoundly incapacitating problems in those suffering from the disorder."

The CDC have also issued advise to sufferers to avoid the use of herbal remedies, such as comfrey, kava, chaparral, bitter orange, licorice root and yohimbe, due to their potential danger.

It is hoped that studies such as these, as well as increasing public awareness and perception of the disease, may help to identify at-risk groups and result in earlier diagnosis and potential treatment. The current study compared 43 patients with CSF with 60 control subjects chosen from a sample of over 56,000 adults in the Wichita area (KA, USA).

The study found that patients with CFS reported a three- to eightfold higher level of exposure to childhood trauma and psychiatric symptoms compared with controls. However, the most notable results were seen in the prevalence of emotional and sexual abuse, which increased the risk of CFS by 77%.

`...as many as 80% of people with CFS may not be aware that they are suffering from the disease as the symptoms, including headache, sore throat and muscle pain, are so common in the general population.'

Christine Heim, lead author of the study, commented that "Not all people with CFS had histories of childhood trauma, and not all of the people who had childhood trauma had CFS." She continued that "It's not the whole picture. There must be some sort of resilience, and if we knew what those were, that would be important for prevention." In addition, Nancy Klimas noted that "It's important to see that CFS has subgroups…it's really important not to merge all these observations into one solid, big group."

A second study examined a group of 19,192 Swedish twins, of which 1570 had CFS. Again, it was demonstrated that those who had experienced emotional stress at an early age were more likely to have CFS, and those who claimed that they experienced day-to-day stress were between 64 and 65% more likely to develop CFS than those who did not.

Data published previously by the CDC in the journal *Pharmacogenomics*, indicated that people who suffer from CFS have a genetic make up that affects the body's ability to adapt to change.

Norepenipherine and the stress response linked to accelerated cancer growth

A report, published in the November issue of *Cancer Research*, has implicated norepinephrine (NE), a hormone involved in the stress response, in cancer metastasis and accelerated tumor growth.

It had already been shown by Anil Sood, of the University of Texas MD Anderson Center (TX, USA), that NE caused the production of matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF) in ovarian cancer cells. These recent findings further illustrate that the effect of NE on cancerous cells is not just limited to ovarian cancer and may well be a common factor in all cancer cell growth and metastasis.

Ronald Glaser of Ohio State University (OH, USA), and lead author of the article, commented "This opens up an entirely new way of looking at stress and cancer that's different from current interpretations."

The researchers treated nasopharyngeal carcinoma (NPC) cell lines with NE to investigate the effects of NE on the expression of two MMPs, MMP-2 and MMP-9, which play a part in cell scaffold breakdown, and VEGF, involved in the growth of blood vessels. As anticipated, following treatment with NE, the cells all produced MMP-2, MMP-9 and VEGF. The group tested several different types of NPC tumors, all of which expressed both the MMPs and VEGF. Glaser commented that "From this we can say that there is a likelihood that all NPC tumors will have these receptors as well."

Eric Yang, a coauthor of the paper added, "MMP-2 and MMP-9 contribute to the aggressiveness of these tumors. It isn't clear exactly how they are operating but they may work with VEGF to facilitate blood vessel growth in new tumors so that they can grow."

The researchers also investigated the affects of propanol on tumor cells following treatment with both NE and noradrenaline, and Glaser pointed out, "This suggests a new approach to possibly fight some cancers – the prescribing of β–blocker-type drugs that would block these receptors and perhaps slow the progression of the disease."

He continued that "Using this approach may not cure this cancer but perhaps we could slow down its growth, making the tumor more sensitive to anticancer therapy, and therefore extending the patient's lifespan and improve their quality of life."

Antimalarial drug shows potential in treating vCJD

A team of German chemists have made an exciting discovery, which may advance the treatment of prion disease.

The rare and fatal human neurodegenerative condition, Creutzfeldt-Jakob disease (CJD), is unique. Prions play the role of the infectious agent, which replicates without nucleic acids, instead inducing the conversion of a normal prion protein to a misfolded isoform. The conversion of cellular prion protein (PrPC) to pathogenic scrapie protein (PrPSc) is conformational.

Previous research highlighted the capabilities of the antimalarial drug, quinacrine, to destroy malformed prions and abolish prion infectivity in cell culture models, but has shown little success *in vivo*. Other drugs proved to be ineffective when applied to prion-infected rodents as they lacked blood–brain barrier permeability.

Heterocyclic compounds, such as quinacrine, an acrine derivative, target lipid metabolism, which controls PrPC conversion. Quinacrine acts as an effective antioxidant and executes its antiprion activity by redistributing cholesterol from the plasma membrane to the intracellular compartment, which causes destabilizing of membrane domains, although the exact mechanism of antiprion action remains unclear. The drug is currently in clinical trials as a therapy for human prion diseases, which are due to end in May 2007.

The team of chemists, lead by Gmeiner, have synthesized 18 novel compounds in an attempt to highlight synergistic antiprion effects. The agents are structural chimeras of quinacrine and the tricyclic antidepressant, imipramine, which also has antiprion activity. The novel class of potential pharmaceuticals have an 'unprecedented' ability to destroy the misfolded proteins and have been shown to greatly increase the antiprion efficacy of quinacrine. A recent study that appeared in the November issue of the *Journal of Medicinal Chemistry* describes the chemical synthesis and bioassays of a focused library of both the compounds involved.

An analog containing an unsubstituted acrine moiety combined with an ethylene spacer proved to exhibit the strongest potency, with an EC_{50} value of 20 nM and full antiprion activity of 75 nM when compared with quinacrine.

According to the National CJD Surveillance Unit, in the UK alone, there have been 150 deaths attributed to the disease since 1990. The nature of the disease, including the late-onset symptoms, make it difficult to treat. In addition, it is not yet known whether the neurodegenerative process can be reversed after the prions have been removed. The synthesis of these compounds is a step in the right direction and provides hope for future drug trials for prion disease treatment.

New research demonstrates the importance of the diagnosis of diastolic abnormalities in patients with heart failure

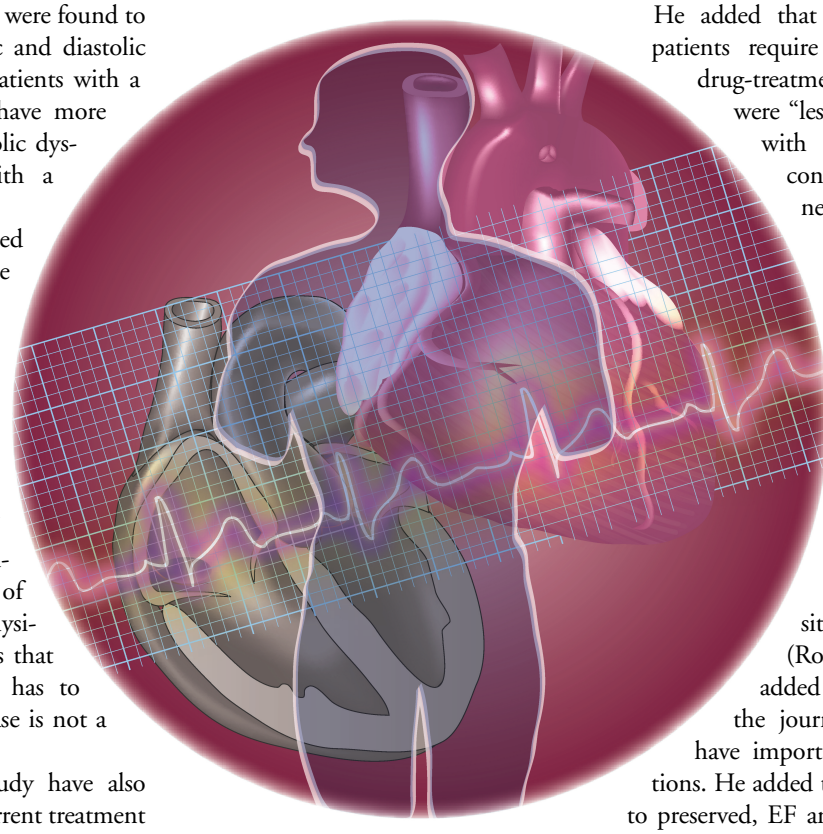
Results from a recent study have revealed that the incidence of heart failure due to diastolic abnormalities is much higher than previously thought. In fact, the study, carried out by researchers at the Mayo Clinic (MN, USA), showed that in a group of 556 people being treated for heart failure, 80% had diastolic abnormalities and 55% had normal or near-normal ejection fraction (EF). In addition, 37% of patients were found to have a combined systolic and diastolic malfunction. However, patients with a low EF were found to have more moderate or severe diastolic dysfunction than those with a preserved EF.

The findings, published in the November 8th issue of *JAMA*, contradict current recommendations to examine for systolic abnormalities in patients with heart failure. Veronique L Roger, Consultant in cardiovascular disease and member of the research group, highlighted the importance of these findings for the physician "What this means is that the practicing physician has to recognize that heart disease is not a disease, but a spectrum."

The results of the study have also highlighted the lack of current treatment options for heart failure due to diastolic abnormalities. Barry Borlaug, Consultant in cardiovascular disease at the Mayo Clinic, commented "This is a major public health problem…half of all heart-failure patients have preserved ejection fraction. There is not much in the way of proven therapies for it. The Roger study shows that mortality for both conditions is the same, about 6% in the course of the study."

Study limitations included a degree of population bias since the patients were identified through Mayo Clinic electronic medical records. In addition, the data is not transferable to under-represented ethnic groups. However, it is hoped that the trial could potentially provide a benchmark for comparison across different populations.

In another report in the same issue of *JAMA*, researchers from the University of California (CA, USA) demonstrated the importance of systolic blood pressure. It found that upon admission to hospital for heart failure, patients with a higher systolic blood pressure had much better outcomes than those whose systolic pressure was low.



The cohort study examined data from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry, which included over 48,000 people treated for heart failure across 259 hospitals in the USA in 2003 and 2004. It was found that the in-hospital risk of mortality increased by 21% for each 10-mm drop in systolic blood pressure.

Gregg Fonarow, Professor of cardiovascular medicine and science and member of the research group, commented on the significance of these findings, "What the results imply is that patients with systolic blood pressure under 120 clearly require more intensive monitoring and more intensive therapy both in and out of the hospital…they remain at high risk for 60–90 days after discharge."

He added that even though these patients require a more aggressive drug-treatment approach they were "less likely to be treated with these agents." He concluded that "We need further research on improving the outcome for patients hospitalized for heart failure with low systolic pressure."

Adding his approval to the findings of these two separate studies, Per Hildebrandt of Roskilde University Hospital (Roskilde, Denmark) added in an Editorial for the journal that the studies have important clinical implications. He added that heart failure due to preserved, EF and diastolic dysfunction deserve the same attention previously afforded to heart failure with reduced left ventricular EF.

These two new studies add important new evidence to the issue of diagnosis, treatment and prognosis of patients with heart failure. The disease currently affects an estimated 15 million people worldwide and is one of the leading causes of hospitalization.

In the UK alone, heart disease and related complications have been estimated to cost GB£29 billion per year, representing 60% of National Health Service spending.