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Saved by stem cells

Sin Jun, five, is alive today thanks to cord blood transplant

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Lee Hui Chieh

The stem-cell hope

Stem cells, which have the potential to develop into some or all of the specialised cells in tissues and organs provide hope that they can replace damaged cells. The race is on to find new ways to harness them to treat various diseases

PHOTO: AFP

Embryonic stem cells seen through a microscope viewfinder in a laboratory in Brazil. These cells are usually taken from embryos that are left over from in-vitro fertility treatments and donated for research by the women.

To most people, a bone marrow transplant is as familiar as any Japanese, Korean or Taiwanese tearjerker, which often features a protagonist who is dying of leukaemia and needs such an operation.

Stem-cell therapy, on the other hand, sounds experimental, almost the stuff of science fiction.

Yet, the bone marrow transplant, which has been in the medical lexicon for decades, is really a form of stem-cell therapy. It is a transplant of haemopoietic stem cells, or immature blood cells, found in the bone marrow.

Bone marrow transplants have been used here since 1983 to treat blood diseases such as leukaemia.

These and other stem-cell treatments here have been done mostly with adult stem cells. These are immature cells found in the body's tissues or organs that can eventually develop into some or all of the specialised types of cells found in those tissues and organs.

The appropriate stem cells are injected into the body to replace diseased or damaged cells.

The race is on to find new and more effective ways of harnessing stem cells for the treatment of various diseases.

For example, the world's first trial of stem-cell therapy in stroke patients was launched about two weeks ago in Britain. The therapy is aimed at reversing disabilities caused by the stroke.

In the first phase, 12 patients will have neural stem cells – grown in a neural stem-cell line using stem cells from foetal tissue – injected into the affected areas of the brain, between six and 24 months after the stroke.

They will be monitored for two years to see if the stem cells can repair the damaged areas.

Researchers worldwide are also studying stem-cell therapy using embryonic stem cells.

These cells are pluripotent, meaning that they can develop into almost any type of cell in the body and can potentially be used to treat a vast number of diseases.

But their use has been controversial as some people object to them on ethical and religious grounds.

The cells are usually taken from embryos that are left over from in-vitro fertility treatments and donated for research by the women.

Human genetic material is also being introduced into animal eggs to form embryos.

Singapore has only general guidelines on stem-cell research, but no national regulations.

The Ministry of Health is drafting a new Bill on stem-cell research, to "ensure that such research operates within boundaries acceptable to society".

The Bill will be ready probably by next year.

The ministry is also studying the possibility of licensing cell- and tissue-based therapeutic services.

In Singapore now, a doctor who performs any form of stem-cell therapy on patients has to ensure that the therapy is backed by scientific evidence and accepted by the medical profession.

Therapy which has yet to be proven or become accepted medical practice can be administered only under a clinical trial.

The trial has to be approved by the hospital's ethics committee before it can proceed.

The quality, safety and efficacy of cell- and tissue-therapy products, like other biological medicinal products, are regulated under the Medicines Act.

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FROM BUBBLE BOY TO BUBBLY BOY

A cough that lasted for two weeks landed Hoh Sin Jun in hospital in early 2006, sparking a 15-month ordeal for the boy and his parents.

After a battery of tests over a few weeks, doctors at KK Women's and Children's Hospital (KKH) diagnosed the five-month-old boy with a rare condition called severe combined immunodeficiency. This is a genetic defect that left his body unable to fight infections.

Sometimes called "bubble boy disease", the condition was made famous by David Vetter, an American who lived for 12 years in a plastic, germ-free bubble and died in 1984 after complications from an unmatched bone marrow transplant from his sister.

A similar fate awaited Sin Jun unless he could get a transplant of bone marrow or cord blood that was a close genetic match.

His father, Mr Hoh Kim Youn, recalled: "We were lost and overwhelmed and couldn't accept the diagnosis."

In the meantime, Sin Jun was infected by the tuberculosis bacteria in his lungs, arm and leg, and needed procedures to remove the infected areas. He also caught a rotavirus, which gave him severe diarrhoea.

Mr Hoh quit his job on a cable ship and his wife, Ms Leong Hong Yeok, left her quantity surveyor job, to look after Sin Jun full time.

Fortunately, a match was found through the public Singapore Cord Blood Bank and Sin Jun became its first recipient of a cord blood transplant in May 2006 when he was nine months old.

He is now an active five-year-old in a school for children with special needs. A side effect of the antibiotics to treat tuberculosis left him hearing-impaired. He has a cochlear implant in his right ear and wears a hearing aid on his left ear.

But since the operation for cochlear implant in September 2008 – his 10th and last one – he has not needed hospitalisation.

He has follow-up checks every three months and is on thyroid medication for life to prevent his gland from becoming inactive.

He gets the occasional coughs and colds, but is otherwise well, said Ms Leong, 37, who returned to her previous job last year.

Mr Hoh, 36, now a service engineer, said of their only child: "We watch him closely and don't let him run around on his own."

His wife said: "Every day, when we see him smiling or asleep, we feel a sense of gratitude."

The transplant given to Sin Jun of haemopoietic stem cells – or immature blood-forming cells contained in bone marrow or cord blood – is now the most established stem-cell therapy.

ST PHOTO: TED CHEN

A cord blood transplant in 2006 transformed Sin Jun, five, seen here with his parents, from a sickly boy unable to fight infections to a healthy, cheerful one.

The stem cells are usually collected from the bone marrow of a relative or an unrelated donor who is a close genetic match.

With advances in technology, they can also be taken from cord blood – which remains in the umbilical cord and placenta after birth – and blood circulating in the body called peripheral blood.

They can be used to treat disorders of the immune system like Sin Jun's, and blood diseases like leukaemia and thalassaemia, in which a genetic defect leads to insufficient red blood cells or oxygen-carrying haemoglobin.

A patient with blood cancer usually has chemotherapy or radiotherapy to destroy the cancer.

The haemopoietic stem cells are then infused into the bloodstream. They then migrate to the bone marrow and develop into platelets, and red and white blood cells.

Bone marrow transplants have been done here since 1983 and are offered by National University Hospital, KK Women's and Children's Hospital (KKH), Singapore General Hospital (
and doctors in private practi

SGH has done over 900 transplants in adults since 19
while KKH has done 97 in ch
between 1998 and this year
largely for leukaemia.

A transplant costs $80,00
$100,000 in a public hospita

Cord blood banking arrive
here in 2001, when private c
blood bank CordLife opened.
was followed by private ban
StemCord in 2002 and Singa
Cord Blood Bank in 2005.

Parents pay to store their
children's cord blood in priv
banks for their own use later

Three leukaemia patients
retrieved cord blood from
CordLife. StemCord has yet t
release cord blood, but abou
cancer patients have had
transplants of stem cells take
from bone marrow and perip
blood.

The public bank accepts
donations of cord blood to b
by anyone in need, but he h
pay $2,000 to test each unit
match, and up to $26,000 to
retrieve a unit.

It has facilitated 65 cord b
transplants here and oversea
others, besides Sin Jun, had
"bubble boy's disease".

NEW SKIN FOR BURNS

Stem-cell therapy has been used here since the late 1990s to grow new skin for patients who have suffered severe burns over 40 to 50 per cent of their bodies.

For such patients, grafts of skin taken from other parts of their body or donated skin will not suffice, as the wounds are so large that there is not enough skin from elsewhere to graft, and too deep for the skin to repair itself, said Professor Colin Song, director of Singapore General Hospital's (SGH) Burns Centre.

SGH treats an average of 12 such patients a year.

A 2cm-wide square of the top layer of healthy skin, called the epidermis, is taken from the patient's groin, and the cells – including some stem cells – separated in the laboratory.

All the cells are cultured on a layer of fibrin – a fibrous protein that helps blood clot – using a medium that allows them to multiply but not develop until they are transplanted, said Mr Alvin Chua, principal scientific officer at SGH's skin bank unit.

Typically, the sheet of skin can be grown from the size of a 50-cent coin to that of about two A4-size papers, over roughly three weeks, he said.

The mucus-like sheet of skin is then transferred onto the burnt skin, which the stem cells will replace.

RENEWED KNEES

Former national netball player Sally Cho (right) was forced to give up the sport 10 years ago when the pain in her knees became unbearable.

Miss Cho, 56, a procurement officer, still played at club level after leaving the national team in 1989.

In the last few years before she called it quits, her knees became swollen and painful after each game.

In 2003, the pain worsened and her knees hurt when she climbed the stairs. One day in 2005, she woke up to find them locked.

She sought help from Associate Professor James Hui, National University Hospital's (NUH) senior consultant orthopaedic surgeon, who sliced her left kneecap and implanted cartilage grown from stem cells taken from her bone marrow into the joint. The cartilage cells grew to fill the spaces between the bones, he said.

ST PHOTO: DESMOND LIM

Miss Cho had the procedure done on her right knee two years later.

After a year of physiotherapy, she is now playing badminton weekly. She said: "Now I can play normally but I don't go all out like before."

She is among more than 200 patients who have paid $4,000 to $8,000 to undergo this therapy, on trial since 2003. Prof Hui hopes to recruit 300 patients aged below 65.

NUH is also testing a second method using stem cells injec
directly into the knee.

Patients first undergo an e
treatment where microfractur
holes made with a tiny pick, a
made through keyhole surger
bone of the worn-out joint. T
stimulates the bone marrow i
releasing a type of stem cell t
later grows into cartilage.

Stem cells are also retrieve
the hip, grown and injected i
knee with hyaluronic acid, wh
protects the cells.

NUH hopes to enrol 100 pa
in this trial, which began last
All of them will get microfrac
and the acid, but only some w
given the additional stem cell
comparison purposes. The 42
patients treated so far paid be
$4,000 and $7,000.

All stories by Lee H

TODDLER NO LONGER IN CONSTANT PAIN

Georgia Conn, aged three, can now sit in a stroller and go for outings with her parents without crying from constant pain.

She can hold her neck up and look into her parents' eyes for a few minutes, without her head flopping over every few seconds.

These little acts that come naturally to other children are achievements for Georgia, who has cerebral palsy, in which part of the brain controlling motor functions has been damaged.

The result of an accident at birth that deprived her brain of oxygen, it left her with physical disabilities, communication difficulties and seizures.

Her parents – bank director Michael Conn, 38, and graphic designer Louise Conn, 36 – credit her progress to an infusion of her cord blood in September last year. She made the news then for being the first here to receive this therapy for cerebral palsy.

Cord blood, which is the blood that remains in the umbilical cord and placenta after birth, contains stem cells that can turn into a variety of cells. Scientists believe that the stem cells can migrate to the brain, where they become neural cells and repair the damaged areas.

ST PHOTO: NG SOR LUAN

After an infusion of her own cord blood, Georgia, three, seen here with her parents, can now hold her neck up for a few minutes at a time.

Georgia's pain threshold has been raised, her muscles have become stronger and she has become calmer, happier and more expressive, Mrs Conn said.

She said: "Initially, we couldn't put her in the stroller or car seat, because she was crying a lot. We thought: 'Gosh, we will never be able to leave our front door.' But now, we can perhaps even go on a holiday."

The Australians, who have lived here for almost six years and are permanent residents, have another daughter, Sybilla, aged one, who is healthy.

They found out about this experimental treatment through their own research and planned to take Georgia to the United States to enrol in an ongoing study by Duke University.

But they realised it could be done here after CordLife, a private cord blood bank storing Georgia's cord blood, linked them to neurosurgeon Keith Goh.

Dr Goh, who is in private practice, said preliminary results from the Duke University study showed that the motor functions of children with cerebral palsy improved after they were injected with their own cord blood.

Even if the $10,000 infusion did not work, it would not harm Georgia as the cells were hers, he said. Dr Goh also treated a Singaporean boy with cerebral palsy. The Health Ministry gave the go-ahead for both cases.

Meanwhile, the Conns have not stopped there. A month ago, they took Georgia to a US clinic for a second infusion, using donated cord blood, at almost double the fee here.

But she still continues with physiotherapy, occupational therapy and an epilepsy drug.

Mr Conn said: "We are not looking at Georgia being cured by stem cells but just at making her muscle injury better. Our experience has been positive."

REPAIRING THE EYE WITH MOUTH CELLS

The surface layer of the cornea can be grown in the laboratory using stem cells from the lining of the mouth.

This is because epithelial stem cells in the mouth are similar to those in the surface layer of the cornea, said Dr Leonard Ang, a visiting consultant at the Singapore National Eye Centre (SNEC), who carried out the first such transplant here in 2005 after being trained in Japan.

Since then, 16 transplants have been done on patients with such severe corneal surface disease in both eyes that they do not have enough healthy eye tissue to patch up the diseased parts that are removed.

In 1999, the SNEC pioneered the transplant of another type of stem cell – the conjunctival stem cell. It develops into the cell of the conjunctiva, a translucent membrane covering the white of the eye.

The stem cells are harvested from the patient's own healthy eye tissue and cultivated. They are transplanted into the eye to replace diseased parts of the membrane, which can be hit by a common abnormal growth called pterygium and tumours.

About 45 patients here have been treated with this method.

Traditional methods involved transplanting tissue from donors or tissue grown from animal cells.

The use of the patient's own tissue in both stem-cell transplant methods minimises the risk of infection and of rejection, said Dr Ang, medical director of Singapore Medical Group's The Eye & Cornea Transplant Centre.

The oldest stem-cell transplant for the eye, that of the limbal stem cell, was pioneered in the United States in the late 1980s. These stem cells, taken from the limbus – the cornea's perimeter – are grown into a sheet and transplanted to reconstruct the surface of the cornea.

Professor Donald Tan, SNEC's medical director, said that the first-year results of these stem-cell transplants, which are all considered experimental, have been good, but the longer-term results have to be studied further.

LITTLE LUCK FOR HEART THERAPY

Efforts to use stem cells to repair heart muscle damaged from heart attacks or heart failure in patients do not seem to have fared well.

About nine years ago, National University Hospital (NUH) started a trial on 20 patients with coronary artery disease, testing the effects of transplanting stem cells into their hearts.

All of them had bypass surgery to clear their blocked arteries. Half of them were also injected with stem cells that had been drawn from their bone marrow.

Five to seven years later, a comparison of the two groups of patients found no significant difference between them in heart function, said Associate Professor Theodoros Kofidis, consultant cardiothoracic surgeon at the National University Heart Centre.

In May 2002, a man had stem cells from his thigh muscle injected into his heart. It is not known how he fared.

But researchers here are not giving up.

In 2005, the National Heart Centre patented a type of stem cell derived from adult bone marrow that can be turned into heart muscle cells.

It hopes to begin a clinical trial early next year, said Associate Professor Philip Wong, director of its research development unit.

All stories by Lee Hui Chieh

Rethinking stem-cell therapy

Associate Professor Theodoros Kofidis

Heart disease may result in heart failure, in spite of modern therapies. The underlying condition in the majority of cases is the insufficient supply of blood to the heart muscle, due to blocked arteries of the heart.

The consequences are heart attacks, enlargement of the heart, thinning-out of the heart muscle, diminished heart function and a patient with reduced quality and length of life.

Every year, millions of new patients are diagnosed with this condition. Current therapies include drugs, bypass and heart valve surgery, assistive devices and transplantation.

Yet, less than 2 per cent of patients worldwide have access to a definitive surgical therapy and even among those in developed countries, many are not operable.

Hence, scientists and doctors alike are seeking new paths to treat advanced heart disease.

Use of stem cells

The one that has ignited the widest attention and investment in the last 10 years is the use of stem cells and tissue engineering to restore the heart muscle.

In tissue engineering, blocks or patches of heart muscle are entirely produced from biocompatible materials in the laboratory and then implanted in the heart to support the heart's structure.

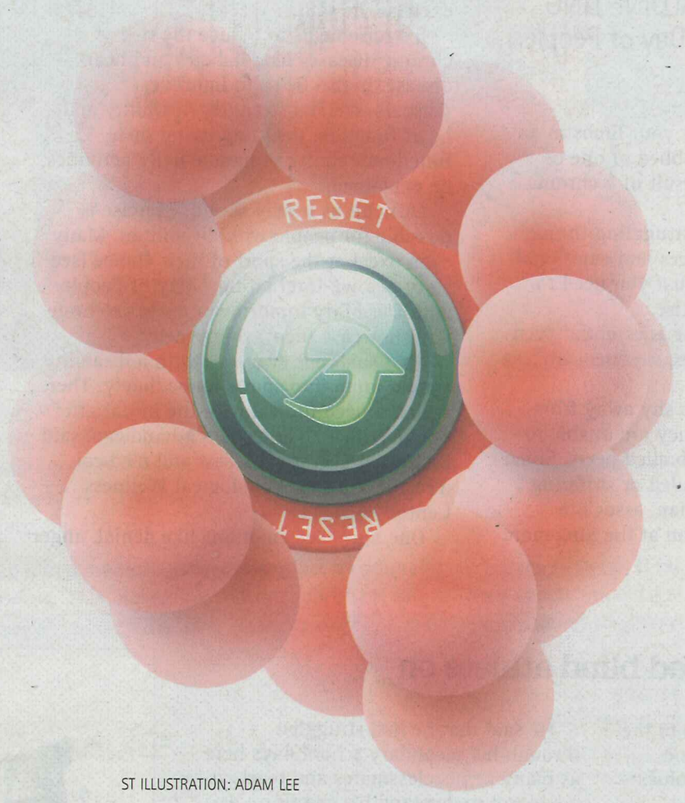
Most of these applications are still experimental and have not been tested on large numbers of patients.

Scientists are also looking to restore the heart muscle using different types of stem cells and different engraftment routes into the heart.

A plethora of stem cells are available, but some have not been cleared for use in humans because they could be rejected by the patient's body, cause cancer or be deemed unethical.

Therefore, the trend is to use stem cells that originate in the patient's own body. These include muscle stem cells, fatty tissue stem cells and blood stem cells.

Equally diverse are the routes through which stem cells can be sent into the heart.



ST ILLUSTRATION: ADAM LEE

One way is to inject them directly into the heart muscle during a heart operation.

Another way is to inject them into the coronary arteries of the heart. A third way is to inject them into the veins or via catheters entering the body through the leg or arm arteries.

All methods have advantages and disadvantages. Some are less traumatic for the patient, but less efficient. Others may cause serious side effects, such as clogging of the coronary arteries or severe irregularities in the heartbeat.

The setbacks

Many clinical trials have been performed since the first one in Germany around 2001.

Some of the reports were enthusiastic and generated the "stem-cell hype" and a huge wave of activity.

However, the trials were often too rushed and not perfectly designed and the results were rather controversial. In many cases, severe complications occurred.

Scientists and doctors have come to realise that years after, patients who had stem cells transferred into the heart did not necessarily perform better than those who did not receive stem cells.

The majority of the stem cells die within the first few days of being injected into the damaged heart. Even if some survive, they do not differentiate to form functional heart muscle cells to replace the lost ones.

The initial hype over stem-cell therapy for the heart has evaporated to a significant degree.

Our team of doctors and scientists feel that we need to hit the "reset button".

We have invested more time in studying the anatomy and structure of the heart.

The heart is a dynamic organ in the shape of a helix (winding ribbon) and consists of multiple, interacting muscle layers. It propels 280,000 tonnes of blood with 3 billion beats during a lifetime. This is very hard to match in the petri dish with a chaotic solution of cells.

We have come to the realisation that it is difficult to treat the heart with stem-cell therapies due to its special structure and pump function, unless some changes in the approach are made.

The breakthroughs

In a series of preliminary experiments on small animals, we showed that inflammation is a major issue during a heart attack. We supplemented stem cells with anti-inflammatory drugs and found that an injection of this mixture improved the pumping force of the heart by several times more than using stem cells alone.

Similarly, adding antioxidants, such as vitamin C, to the stem cells or engineered tissue blocks significantly increased stem-cell viability and tissue engraftment in the heart. The function of the heart also improved.

The most impressive breakthrough came when we simultaneously injected stem cells and liquid tissue compounds into the heart. This method achieved large-scale restoration of both the viability and architecture of the heart muscle and the engraftment of stem cells.

Recently, our team received a grant from the National Medical Research Council to carry on with these experiments on large animals, one step before testing on humans.

These experiments will be carried out endoscopically – using instruments inserted into the body through small cuts that let doctors see its interior and perform surgery. This will simulate simple and safe day surgery on humans.

Hopefully, in this way, a large number of patients can be treated in future with a first-line therapy that has a long-term effect.

At this point in time, we consider stem-cell therapies for the heart a promising new field in which the risk and benefit ratio needs to be carefully weighed.

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Associate Professor Theodoros Kofidis is a consultant cardiothoracic surgeon from the National University Heart Centre, Singapore. He is also the chairman of its Initiative for Research and Innovation in Surgery.