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SMA NEWS

Stem Cells – Singapore Style

By Dr Toh Han Chong, Editorial Board Member

What is a stem cell? If you asked a Singaporean-in-the-kopi-tiam this question before the new millenium, you might get answers like, "It's the juicy stuff you suck from bak kuh teh!" Or "Wah piang, stem cells? Liak boh kiew!" (Translated into English as *"Good gracious, stem cells? I absolutely catch no balls!"*)

In the new millenium, the mass media has made stem cells as sexy as Renee Zellweger in *Chicago*, as real and round as Renee Zellweger in *Bridget Jones' Diary*, and as emotive as Renee Zellweger in *Jerry Maguire*. Kiasu Singaporean parents will make sure their budding scientist children know how to define "stem cell" in their second language. Profiteers will want to add stem cells into fruit juice blends and herbal soups as health boosters and aphrodisiacs. But stem cell hyperbole is looking more like hamtam bola as many stem cell start-up companies worldwide have taken hard hits from nervous Big Business looking for stem cell magic to pull a fast rabbit out of a hat for quick profits and not just speculative promises. With stocks in stem cell companies dropping, venture capitalists are demanding, "Show me the bunny and money! Show me the spinal cord regeneration! Show me the cure for diabetes!" Is the stem cell magic just smoke and mirrors?

STAYING ALIVE

So what is a stem cell? It is very small, it can renew itself, it has the potential to live forever and it can totally transform into a different cell type in a process called transdifferentiation and then truly function like that cell.

During that tragic weekend of the RSS Courageous collision, I was holidaying in Bintan and saw a map of the Indonesian archipelago. It struck me again that Singapore was smaller than Batam and Bintan, a dot on the archipelago. But Singapore has a productivity output higher than much larger countries. With its smallness, ability for self-renewal, precious little resources, and a regulating central machinery, it looks uncannily like a stem cell – the complexity of which we are only beginning to uncover. Being young, with less homogenous character and culture unlike a huge glob of fat, or a large industrial liver, or even a mighty heart, the stem cell survives and stays relevant by tireless self-renewal and the knowledge-driven feat for transdifferentiation and plasticity.

Can Singapore remain relevant, transform and export to the global organism? How does a tightly controlled cell let its hair down, get creative and switch form and function so magically? In this stem cell ecosystem, there is going to be individually empowered proteins and nimble processes jive talking with one another, which drives cell survival and plasticity in a most fascinating way. This is one of the holy grails of development biology and all of life sciences.

RUN TO ME

Stem cells are of two types – embryonic stem (ES) cells and adult stem cells.

ES cells are extremely versatile and can live forever. They have been called the mother of stem cells and are derived from embryos.

Adult stem cells were believed to be less immortal, less versatile but could still live for very long. Until a major breakthrough in year 2002 from Dr Catherine Verfaillie's University of Minnesota team. In a conference hall in Seoul, Korea, I attended her plenary lecture about this amazing non-haematopoietic stem cell obtained from adult bone marrow cells that could stay forever young like ES cells, and could transform magically into any cell of choice. She called these cells multipotent adult progenitor cells (MAPC). Scientific purists have argued that while there are many scientific studies that infer stem cells can transdifferentiate into another cell type and function as that designate cell, there are far fewer proof-of-principle single cell experiments that absolutely demonstrate one stem cell can become a fully purposeful neural cell secreting dopamine or cardiac myocyte cell helping to pump the heart. In other words, such an experiment would be akin to filming clear footages of mild-mannered reporter Clark Kent get into a telephone booth and transform into Superman who can then leap

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tall buildings with a single bound. The issue of differentiation and plasticity of adult stem cells has been further thrown into debate because of two studies published in the journal Nature in April 2003 which showed that mice with a fatal liver disease were cured from a bone marrow transplant not because of differentiation of the bone marrow stem cells to liver cells, but by cell fusion.

Just as you can find a Chinese restaurant in almost any part of the world, you can find stem cells in almost any part of the body, commonly in the bone marrow, in the umbilical cord blood, in the adult blood, and more unusually in adipose tissue and dental pulp.

The one type of stem cell that has decades of proven clinical value for treating disease is the adult blood stem cell from the bone marrow. If a human bone marrow is lethally irradiated either catastrophically in a nuclear accident or intentionally to eradicate a cancer like leukaemia, and infused with either his or her own blood stem cells, or from a genetically similar or even dissimilar donor, these blood stem cells will home in on the bone marrow and repopulate it and grow red cells, white cells and platelets. Even blood stem cells from a xenogeneic animal source has been proven to repopulate the bone marrow of a totally different species, such as pigs to rats. How does this homing instinct happen? Just as you may ask, why do Singaporeans anywhere in the world home in on a "char kuey teow" stall, or why are fanatical female fans always able to sniff out an F4 boyband member? Many scientists are working on this, as it will be powerful knowledge to know how, for example, a blood stem cell can home in to the pancreas and start producing insulin as β cells. But more importantly, it may teach us how to become as irresistible as F4 idols.

MASSACHUSETTS

As a clinical fellow at the Massachusetts General Hospital, I had the privilege of looking after Janet M, a bubbly fifty-something platinum blond with incurable resistant multiple myeloma and related end stage renal failure. She had just received a combined bone marrow stem cell transplant and renal allograft transplant – a world's first – where a mild conditioning regimen allowed for the stable mixture of her own blood stem cells and her sister's donor blood stem cells in the body. This is called a mixed chimaera achieved by a pioneering therapy called minitransplant. Once this mixture of white cells enters the thymus, they are tricked into thinking that each donor and host cell actually does belong to the body and any T cell clone that reacts adversely to the perceived "self-proteins" is deleted in this school for white cells. Tolerance is achievable, which prevents organ rejection and graft attack of the patient's normal organs. Peripheral immune tolerance is also at work. At a later time, anti-cancer donor T cells were given to eradicate her cancer. Janet was taken off cyclosporine completely in less than three months, her myeloma is in remission after five years, her allograft kidney is doing just fine and she is over the moon. This happy story illustrates how far we have come in clinical research on blood stem cell transplantation, and its surprising application in the field of organ transplant, and in the fight against cancer with immune cells.

One day, when we can clinically use a ready supply of ES cells or adult stem cells to repair damaged brains, hearts and cartilage in patients, these stem cells are likely to be immunologically distinct when they mature in the host body. This means the host immune system will react against them and potentially destroy them. How do we make the body tolerant to these incoming ES or adult stem cells? The creation of a stable mixed chimaera to induce an immune tolerant state by minitransplant is one possible solution. Other scientists have suggested knocking out the major histocompatibility complex (MHC) genes from these selected stem cells to be used for regenerative treatment, creating a null cell, so making these stem cells "invisible" to host immune surveillance. But non-MHC proteins can still be a red flag to activate immune rejection. Yet another idea is nuclear transfer technology or therapeutic cloning where the host/recipient nucleus is inserted into the donor cell line. This sounds logical once the technology is refined, but cytoplasmic influences of the donor stem cell may still be an immune red flag, creating a danger signal to the host immunity, yet again. All these concerns may be bypassed if Catherine Verfaillie's MAPC stem cells can fulfil its early promise. Then we can just obtain bone marrow cells from patients themselves, coax these cells to differentiate in dishes and work for the patient's tissue and organ regeneration.

HOW CAN YOU MEND A BROKEN HEART

In the late 1990s, I was in a Houston, Texas, lab as a research fellow. In the next-door Margaret Goodell lab, some amazing stem cell wizardry was taking place. This stem cell lab was creating liver cells and repairing myocardial tissue and damaged coronary arteries in mice with heart attacks. Margaret Goodell was first to identify a unique bone marrow stem cell which could transform magically and showed great plasticity. She called it SP cells, which stands for *side population* cells and which are *"seepeh powerful"* cells. Across the street at the Texas Heart Institute, Dr James Willerson and his group were injecting, directly into the myocardium, bone marrow stem cells extracted from the patients themselves who had ischaemic heart disease and severe heart failure, and observed significant improvement in left ventricular function in these patients compared to control patients.

In the Goodell lab was a German postdoc called Gerald who looked like a lanky adult Harry Potter. He described a

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cancer stem cell that had the same characteristics as the SP cells, one of which was a disturbing ability to pump out chemotherapy, and so making these cells chemotherapy-resistant. Recently, breast cancer stem cells were identified, revealing a tiny population of these cancer-initiating stem cells distinct from more mature breast cancer cells. This may partly explain the reason for the limitations of chemotherapy in totally eliminating many advanced cancers. The similarities between stem cells and cancer cells are uncanny – they are both immortal, they can both self-renew and they like to travel to other sites and work their magic or destruction respectively. In fact, if ES cells are injected into animals, they can form benign cancers called teratomas.

Cancer cells could have once been amazing and creative stem cells gone wrong – a kind of cellular Fallen Angel. Why would stem cells mutate to the dark side? A strand of DNA gets sabo-ed by the dark forces of exogenous agents 10,000 times a day. Could young stem cell DNA be more vulnerable to this seige? If you ask Jack Neo, the wise man of Singapore comedy, what the similarities between stem cells and cancer cells are, he might say, "Shh...I notch know, leh...!" And Jack Neo would be right, yet again! "Shh" (sonic hedgehog) and "notch", as is nucleostemin, are key genes that drive both the stem cell and cancer cell. It has been a challenging battle eliminating cancer completely because cancer cells not stupid, and researchers sometimes feel that "money no enough".

SATURDAY NIGHT FEVER

In the movie "The Boy in the Plastic Bubble", a young pre-disco John Travolta played a real life boy with X-linked Severe Combined Immunodeficiency (SCID) Syndrome who died young. In a year 2000 study hailed as the first ever successful gene therapy human clinical trial, bone marrow stem cells were transduced with the SCID gene by means of a defective retrovirus vector, and the transduced stem cells were reinfused into the young patients. Of the nine patients treated and cured, two developed iatrogenic acute leukaemia. This shocked the medical community. Subsequent similar clinical studies were halted. This cautionary tale illustrates just how much more we need to understand the consequences and dangers of manipulating stem cells. Even in using human embryonic stem cells for clinical studies, there is concern that human ES cells are grown on mouse stem cell feeder layer in vitro. The mouse feeder cells could potentially carry dangerous animal viruses into the human host with devastating result. Hence, the recent success of using human feeder cells for ES cell culture by Professor Ariff Bongso was a great leap forward in making clinical application safer.

TRAGEDY

The fanfare which met with the cloning of Dolly the sheep fell more silent when Dolly became wobbly with arthritis and died early from a retrovirus-induced lung cancer. Reproductive cloning should never be allowed and its methods are far from perfect. Up to 30% of cloned species develop genetic defects. In a brave new world, where reproductive cloning is sanctioned, there may arise enticing internet companies like clone-a-babe.com. Clone-a-babe.com promises to clone your favourite girl for a fee. Pimply teenagers with raging hormones will jump at the chance to clone the likes of Elizabeth Hurley or Zoe Tay, realising that these stars would be far too wrinkly when they grew up to the prime of their lives as thirty or forty-something males. Why not clone their girl of choice, so that when the clients reach the prime of their lives, they can court a young, babelicious Liz or Zoe? But the company web information omitted to mention the possible 30% genetic defect rate. So instead, Chin Hor Nee the Teenager who paid $5000 to clone a babe might end up with "Zoe *Kah-Tay*" (or Zoe with dwarfism) or "Elizabeth *Burley*" who turns out to have acromegaly. Sorry, no refund.

HOW DEEP IS YOUR LOVE

One of the least known but most moving movie moments, to me, is from a BBC production called *Life Story* starring Jeff Goldblum as James Watson and Tim Pigott-Smith as Francis Crick – about their discovery of DNA. In the historic moment they revealed the double helix, the cinematography played on this divinely simple, beautiful yet powerful geometric structure that is the key to life in an age of uncertainty. There were tears welling in the eyes of Max Perutz and John Kendrew as they realised how profound this discovery was. Yet the knowledge of DNA that has led to so much great good can also be used for abuse. So too, with stem cells. In the playground of Life, the ominous combo of Power and Pride disguised as Progress tends to yank the sand bucket of goodies from the hands of Truth and Reason. We have derived some of our best medicines from Nature. These include digoxin from foxglove, aspirin from the willow bark, antibiotics from fungus, and cancer chemotherapy like vincristine from the periwinkle, paclitaxel from the Pacific yew tree, and etoposide from the root of the mystical mandrake. Now we may be able to derive powerful medicine from our own cells. In deciphering, interpreting and applying the scriptures of stem cell truths, should our moral sphere play servant to our quest for physical self-preservation?

Whether stem cell therapy will be widely accessible and impact the health of millions like clean water, hand washing, salt and sugar solution, vaccination, antibiotics, and good primary health care, or whether it will be sexy medicine in the preserve of super-specialists, is yet to be seen. In an uncertain world where ancient diseases return to haunt us and new diseases emerge, new medicines will always be a blessing. The understanding of the stem cell and its secrets will open up a whole new way medicine will be practised in the future. ■

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