

The Return of Prometheus:

SAVE and STORE Your OWN STEM CELLS: Implications for Regenerative Medicine

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Stem cells available for tissue regeneration are of three types: Embryonic stem cells (from the inner cell mass of a 5-7 day embryo), Fetal stem cells (from an aborted fetus of less than 3 months of gestation) and Adult stem cells (*bone marrow* (BMSC), *umbilical cord blood* (UCB) or, *peripheral blood* (PBSC)). The first two categories of embryonic and fetal stem cells respectively raise ethical and moral concerns beyond the scope of this article and will thus not be reviewed here. Moreover, the development of cancer from their use remains a crucial issue. **In the present article, all treatments, current and future, all references used pertain to ADULT Stem Cells only.** This is a conscious effort to create a clear definition and enable an understanding of what scientists are debating. At all times when the public is addressed the speaker/author must clearly define what kinds of stem cells are being debated to avoid confusion and conscious or unconscious misleading of the public. So, from now and on, no reference will be made to embryonic or fetal stem cells.

Adult Stem Cells

When discussing Adult Stem Cells a further distinction must be made on the type of cells used and the type of treatment that is given. Adult Stem Cells have been used routinely for almost five decades to repair tissues and organs damaged by injury or disease, most notably haematopoietic stem cells (HSC) taken from *bone marrow* (BMSC), *umbilical cord blood* (UCB) or, increasingly, from *peripheral blood* (PBSC) mostly to replace a diseased bone marrow. The first bone marrow transplantation happened by Sir E.D. Thomas in 1957 and he subsequently was awarded the Nobel Prize in 1990.

Cord Blood from rags to riches?

We all develop from one single totipotent stem cell (able to develop towards any type of tissue) and our human body harbors adult stem cells since the first day of our lives and into long age. Those adult stem cells participate in the everyday well being and conditioning of all our tissues and organs aiding and promoting repair and regeneration. Initially and immediately at birth, blood from the umbilical cord can be easily collected and adult stem cells can be separated and cryo-preserved in the form of Umbilical Cord Blood (UCB) stem cells. This in Thailand can happen if enrolling for the baby services of THAI StemLife. Then the prospective parents will receive a collection kit to take along to the hospital so that the delivering doctor can collect the blood from the umbilical cord and thus ensure that their precious new family member gets a second chance should disease strike later in life. Those UCB stem cells are the source most readily available worldwide without pain or risk for the involved parties (mother or baby), most cost effective and without ethical considerations. Cord blood is no longer considered to

be a biological waste byproduct but is instead already recognized as a major source of haematopoietic (that make all blood cells) stem cells for use as a standard of care in pediatric haematological bone marrow transplantation. UCB stem cells are immunologically naïve and privileged offering distinct tolerance and tissue compatibility advantages over other stem cell sources meaning that tissue compatibility mismatch is tolerated better if the stem cell source is cord blood compared to bone marrow or peripheral blood.

Cord Blood is a rich source of stem cells and is thus considered to be a potential source of cells for future regenerative therapies apart from the conventional bone marrow transplantations that are nowadays standard if stem cells have been collected and are available! If not then chances are slim finding a match as we will see further on. Cord Blood carries distinctive advantages including collection at no risk to the donor (mother or child), greater accessibility for storage, immediate availability in a bank, frozen in small volumes, easy transport, wider availability and relatively low risk of graft-versus-host disease (rejection) despite tissue mismatch, making it possible to find cord blood units for patients with less common tissue types, such as those in racial and ethnic minorities, mixed ethnicity individuals, and lower to zero contamination. Remember those "luk krueng" babies? With beauty along comes rarity as tissue antigens come from two different ethnicities so the new tissue type resulting after the rearrangement of genetic material will be a really rare one, making it difficult to find a match if cord blood has not been kept in advance. In 2004 only 2.6% of the samples at the National Marrow Donor Project (NMDP) come from mixed ethnicity individuals. Cord Blood has clearly gone from biological waste product to an important source of stem cells for use in stem cell bone marrow transplantation. In the childhood setting, available data clearly establish cord blood as a standard of care, now having surpassed the use of bone marrow and peripheral blood stem cells. Even in the adult population the medical community's interest in cord blood as a source of stem cells is increasingly positive as experience increases and high quality cord blood samples are being collected. Single cord blood units can reconstitute entire blood systems in adult patients. Cord blood has the further advantage that it is not subject to the social and political controversy related to embryonic and fetal stem cells. Cord blood stem cells include cells capable of differentiating into connective tissue such as bone, cartilage adipose tissue, heart, muscle insulin producing cells and neural tissue.

UCB is used currently in transplantation for blood malignancies (among others acute leukemia, chronic myelogenous leukemia, myelodysplastic syndrome, lymphoma) and non malignant diseases

such as genetic diseases of the oxygen carrier hemoglobin, inborn errors of metabolism, immunodeficiency states and bone marrow aplastic states but future uses judging from the experimental results of cord blood research seem stunning. Today more than 72 diseases of the bone marrow can be successfully treated by cord blood stem cells. Furthermore, the increasing use of Preimplantation Genetic Diagnosis (PGD and PGD-HLA) in IVF may further widen the use of cord blood stem cells even more! Preimplantation Genetic Diagnosis offers the possibility to the aspiring parents to make sure that genetic diseases present in their families (themselves being carriers knowingly or not) do not appear in their offspring before the embryo is transferred to the womb of the mother. A wished second child may also be conceived to save the life of the firstborn resulting in a family with 2 healthy children rather than one diseased only!

Why so much controversy about who should store UCB?

Regardless of type of use (bone marrow transplantation or cellular therapy) or source of adult stem cells (cord blood, bone marrow or peripheral blood) discussions have focused on issues of safety and solidarity/donation. Controlled studies are being conducted worldwide assessing the safety and feasibility of cellular treatments but let us always bear in mind that proof of concept has been laid 50 years ago in the bone marrow transplantations. It is self explanatory in academic medicine that patients treated with such newer methods must be included in rigid research programmes subjected to local ethical committee approvals before guidelines for treatment will be amended by the international medical bodies and commercialization can occur.

Solidarity and volunteerism among members of a society is an integral part of a society's coherence and should at all times be promoted. Creation of public bone marrow registries and public cord blood banks must be a part of every modern health policy programme of every modern state. But let us not forget that in more than 80% of all bone marrow transplantations worldwide, the stem cells used come from the patient herself or her immediate family so, privately funded stem cell banking programmes will also exist catering to the particular needs of a family (own stem cells, stem cells from siblings and other family members), similarly to private insurances and hospital care programmes and in order to share the costs of such an endeavor that otherwise would significantly burden an already strained public sector. Cord blood banking is of three types i.e. public, private or hybrid. A woman can donate cord blood for unrelated recipient to public banks (unrelated allogeneic transplantation). Private (commercial) banks, on the other hand, offer expectant parents the option to store cord blood

for possible future use by that same child (autologous own transplantation) or for use within the family should HLA matching permit it (syngeneic/related allogeneic transplantation). Hybrid banks can be public banks offering a private service or vice versa. Some public banks seek private banking as a profit making way to finance burdened and crippled public services while some private banks see the magnificent potential of huge numbers of stored autologous samples and divide cord blood samples in half, keeping one half for family use and the other half made available for public use, a scenario that is very real in the eve of cord blood stem cell expansion techniques where even a small part of an own stored sample can be amplified and used for others. Regardless the type of cord blood banking, strict regulations in advertising and quality assurance following local as well as the international Federation for the Accreditation of Cellular Therapy (FACT-NETCORD) guidelines must be endorsed.

Caveat Emptor or Caveat Donor? (Let the Buyer Beware or Let the Donor Beware?)

At no point family cord blood or peripheral blood stem cell storage is a threat to donations as currently in the United States, private UCB collection and storage is performed in less than 3% of all deliveries with a similar situation in Thailand. Such a low rate would probably not have a significant impact on the number of cord blood units available for allogeneic transplantations, although this could change with the increased rate of private cord blood collection. In recent Canadian paper, more than half of the future mothers reported poor or very poor knowledge about cord blood banking but all wanted to have information on this issue by a health care professional. Most of the women would elect to donate to a public bank citing altruism and costs as reasons and a much smaller proportion (14%) would elect private banking. The cost of private cord blood banking would need to drop substantially to influence the preference for public banking, as high income was not a significant factor in the choice between private and public banking. These findings present a formidable challenge for the public sector in educating future mothers early to maintain altruistic attitudes while improving knowledge of cord blood banking in this important group. Education must be thorough, transparent and unbiased not allowing any room for implied understanding and should come early in pregnancy so that parents have adequate time to contemplate their choices. It must inevitably convey risk probabilities and risk management, make comparisons to everyday risks in order to enable lay understanding and also cover the issues of stem cell plasticity and future applications as well as potential treatments with cord blood stem cells to ensure that an informed consent for donation or self storage is really "informed" and can ultimately be legally valid.

Imagine the parental impact of studies showing effectiveness of cord blood stem cells in juvenile diabetes or in the treatment of cardio- and cerebrovascular diseases, osteoarthritis, Alzheimer's, spinal cord injuries or traumatic/hemorrhagic brain injuries. All those situations are not simple ungrounded hypotheses without evidence but ongoing research projects and a growing body of evidence around the world undeniably already showing promising results and tantalizing perspectives.

Risk management and risk understanding: putting it in perspective

The idea of providing a newborn child with an 'insurance' against devastating diseases is obviously highly welcome. Critics against private storage stress that most privately stored samples will never be required since only one in 20,000 children up to the age of 20 will need it but such a probability has never been substantiated with a valid reference and calculation. Moreover, how do we evaluate use or need? Do we do so by following today's applications or should we also focus on future possibilities? On the contrary substantiated numbers with present day epidemiological and treatment data show the risk of developing cancer during childhood to be 2 per 1000 and the likelihood of any such child requiring HSC transplantation for treatment of cancer to be approximately 1 in 2000, not including other less common indications such as aplastic anemia. Others have calculated the probability for an autologous transplant before the age of 20 to be 1 in 2,703 and evidence shows that one-fifth of stem cell transplants are carried out in young people with leukaemia. Moreover, the Australian Bone Marrow Registry reported in 2005 that there were approximately 900 transplants annually in Australia and New Zealand, with most being autologous (a person's own) cells. An even more recent study from Australia and New Zealand shows similar trends with more than 70% of all stem cell transplants in 2004 being autologous (using one's own stem cells) with an age range from 8 months to 78 years while more than 80% of the allogeneic (somebody else's stem cells) transplants are from related sources within the immediate family. What would those patients in need and their doctors have used had the patients kept their cord blood at birth? Avoiding the circulatory burden of a collection later in life when cardiac cellular therapy is contemplated, the risk of a dry tap in an established bone marrow disease as well as the senescence and perhaps impaired functionality of bone marrow or peripheral blood stem cells are indeed major issues. The time required for clearing an allogeneic (donated) transplant is between 3 and 6 months while the impact of waiting in disease progression remains speculative. Observe that the number of transplants performed in a society is not an indicator of transplant need or a transplant risk estimate but merely reflects the efficacy of a health care system. Simply put, if stem cells are available then a

transplant is only possible if the expertise and infrastructure exist to realize it. Conversely, all the expertise and the all best infrastructure in the world stand helpless if stem cells are unavailable!

Is it a theoretical only possibility if the parents of a diseased child in need of bone marrow transplantation seek damages stating that they were not informed about keeping cord blood stem cells at birth for their newborn?

It is all in the Blood!

Those of us that are a bit older and have forfeited the possibility to keep their own cord blood stem cells must be reborn? Not really as collecting and storing your own adult stem cells from your own peripheral blood is an easy exercise! The bone marrow needs to be stimulated for 4-5 days with a substance called G-CSF, which is to be found normally in our body, in order to produce more stem cells and force them out in the peripheral blood thus making it easy to be filtered by a machine called leukapheresis. Blood loss is minimal, no hospitalization is required and the procedure takes 4-5 hrs in a quiet room along with friends and relatives! No more pain or discomfort than as in a regular blood donation is involved. A normal check up needs to be done before in order to make sure that no uncontrolled diseases are present. The procedure is approved by all relevant authorities and is the same procedure used in collecting stem cells for bone marrow transplantation. The difference is that it is our OWN stem cells and will be frozen for our future use.

The return of Prometheus: Old Diseases, New Paradigms

The clinical needs and challenges in the 21st century created by changes in longevity and lifestyle, notably Diabetes, Cardio- and Cerebrovascular disease, Neurodegenerative diseases (Parkinson's and Alzheimer's) and Joint ailments may have found new treatment paradigms in the face of adult stem cells. *Myocardial (heart muscle) regeneration* via direct implantation of adult stem cells in the myocardium in patients with acute or chronic ischemic heart disease seems as an exciting and possible new therapeutic modality. Myocardial regeneration is otherwise not possible with current conventional treatments. *Diabetes and diabetic ulcers* due to critical limb ischemia irrespective of etiology seem responsive to adult stem cell treatments either as bone marrow transplantation in the former or as direct muscle implantation in the latter. Instillation of adult stem cells within the pancreatic irrigation system has been reported with success and this seems feasible given the latest findings that peripheral blood stem cells harbor populations with potential to be insulin producing cells. THAI StemLife along with leading hospitals in Bangkok and under the sponsorship of the

National Innovation Agency (NIA) at the Ministry of Science and Technology is researching the use of peripheral blood stem cells in treating diabetic ulcers, a research with excellent results and that has given us the prestigious award "Top Innovation of Year 2006". *Cirrhotic liver disease* may in the future see hepatic parenchymal regeneration of prometean proportions via adult stem cells instillation in the hepatic artery or in the venous hepatic system. *Stroke* and *spinal cord injuries* may be successfully alleviated via bone marrow or peripheral blood stem cell infusions in the lesions or in the CSF. Autologous haematopoietic stem cell transplantations for *autoimmune diseases* such as SLE, rheumatoid arthritis, other connective tissue diseases and multiple sclerosis have been taking place for years but have now evolved from an experimental concept to a clinically feasible and powerful therapy for selected patients with severe disease with improved engraftment and remission rates.

CONCLUSION

Our bone marrow is a magnificent factory renewing the constituents of our blood system regularly and increasingly appears to be a reservoir of immature cells that can possibly take part in various regenerative and repair functions in our body. The levels of circulating stem cells, being important indicators of cardiovascular disease have only recently been recognized as such. For more than 50 years hematopoietic stem cell transplantations have been performed and are now standard of care mostly using autologous and related allogeneic adult stem cells. Proof of concept, safety and feasibility that non modified autologous and allogeneic adult stem cell transplantations may also be used to treat diseases other than those intrinsic to the bone marrow are abundant in the literature and randomized studies are continuously being conducted with promising prospects at sight. Umbilical Cord Blood is no longer considered to be a biological waste byproduct but is instead already recognized as a major source of haematopoietic and mesenchymal stem cells for use as a standard of care in pediatric haematological bone marrow transplantation. Even in the adult population the medical community's interest in UCB as a source of HSC for larger recipients is increasingly positive as experience increases and high quality UCB samples are being collected. Moreover, UCB is increasingly viewed as the capital ingredient for future cellular therapies in regenerative medicine and may revolutionize the way we treat our society's major ailments and medical threats without causing any heated ethical debates. The discussion should focus on early parental education on available alternatives and on the ethical dilemma created by the possibility of discarding UCB rather than on who should store it. In this aspect the public and private sectors

already in a harmonious, symbiotic and synergistic relationship in patient healthcare will have to cooperate in similar fashion to share the burden in providing cord blood and adult stem cell banking services and to ensure the best available standards for the parents about to have a new family member. Ultimately it is not only a family minimizing personal risk but in the long run a society minimizing public health care costs and ensuring a healthy and thriving population.

In conclusion, advancements in basic and clinical research on adult stem cells (UCB and PBSC) start revealing their potential therapeutic use in regenerative medicine. Aged, damaged, or lost cells could regenerate and their tissues/organs can be repaired by autologous cell-replacement therapies. Yet incurable genetic and degenerative disorders in the human body can be reversed and even cured by the use of adult stem cells and/or their further differentiated progeny. The therapeutic potential of adult stem cells is enormous and in front of us to grasp but in order to fully exploit this potential we must have the main ingredient, which is our OWN stem cells, already stored at a young and healthy age.

For more information on THAI StemLife please visit www.thaistemlife.co.th or email at info@thaistemlife.co.th