



# CHAPTER 1

# 1 Introduction

Stem cells and their therapeutic applications have received much attention around the world. This is due in part to the immense therapeutic potential that these cells harbour, and also to the sea of misinformation that leads to exploitation and malpractice in the current absence of adequate legislation.

South Africa has had limited exposure to stem cells and their applications. While any exploitation is detrimental to the field of stem cells, South Africa is particularly vulnerable to such misuse. Circumstances are already precarious due to a lack of information and understanding (discussed in Chapter 2). This in turn, cultivates fears born out of existing superstitions, cultural beliefs, rituals and practices. Certain cultural or religious concerns could potentially hinder the effective application of stem cell therapies in South Africa and novel ways of addressing these concerns are necessary. This invokes a paradigm shift: Regenerative medicine is an emerging field that requires a holistic approach through novel inter-disciplinary collaborations between empirical science, social science, ethics, religion and culture (discussed in Chapter 3). Understanding how scientific progress and its implementation will affect each individual and consequently the community, will be of cardinal importance to the success of the field. A failure to understand the ethical, cultural or moral ramifications when introducing new scientific concepts could hinder the efficacy and speed of bringing discoveries from bench to bedside. Neglecting proper procedure for establishing the field, would lead to the need for a lengthy recovery of public support in South Africa.

South Africa could benefit from potential therapeutic applications that stem cells have to offer. Two particular burdens that put the healthcare system under strain are 1) a large unmet need in South Africa for bone marrow transplantation to treat malignant and inherited haematological disorders; and 2) the high rates of HIV-1 infection in the population. Both of these elements require larger studies of enquiry to fully elucidate and potentially relieve these burdens. For this reason, the work described in Chapters 4 to 8 is composed of components that form a part of both of the larger studies.

## **1.1 Addressing the need for BM transplantation in SA: Background to the larger study and specific components involved in the current investigation.**

The large unmet need for BM transplantation in South Africa necessitates the use of alternative resources for treatment (Crookes et al., 2007). Umbilical cord blood (UCB) is an important source of stem cells for treatment of haematological and non-haematological diseases and South Africa can benefit greatly from storing UCB SCs in a public UCB SCB.

The larger study therefore has as its goal, to investigate the feasibility of establishing a public umbilical cord blood stem cell bank (UCB SCB) in South Africa. The study consists of five components: (a) public response to the establishment of a public UCB SCB; (b) testing UCB units for HIV-1 (required for compliance with international regulatory standards); (c) flow cytometric analysis for enumeration of CD34+ UCB stem cells; (d) mapping of HLA genotypes/alleles; and (e) an economic feasibility study. Combined results from each of these components will determine the final feasibility of establishing a public UCB SCB in South Africa. The objectives pertaining to the work presented in this Thesis, have to do with points (a) and (b) above.

- (a) Public support for and interest in a public umbilical cord blood stem cell bank (UCB SCB) is a prerequisite to establish a sustainable public UCB SCB. Therefore, public preparedness and support for a public SCB was evaluated in this study, by addressing pregnant mothers attending the ante-natal clinic at the Steve Biko Academic hospital in Pretoria. An initial enquiry led to the initiation of a pilot study (Chapter 4), followed by a principal study into the public's response to UCB banking (Chapter 5).

In addition to the findings of the investigation into the public's response to establishing an UCB SCB, other important considerations include screening UCB units for infectious diseases, and in particular in the South African context, Human Immunodeficiency Virus (HIV-1). South Africa has a high prevalence of Human Immunodeficiency Virus / Acquired Immunodeficiency Syndrome (HIV/AIDS). There remains a risk of obtaining HIV-1 positive UCB through vertical (trans-placental) transmission of HIV-1, if a mother is in the latent phase of HIV-1 infection at the time of birth. This necessitates the implementation of additional safety and quality control measures for collection and screening of potential UCB units, prior to storage or distribution. Should a public UCB SCB be established in SA, all UCB units would need to undergo routine infectious diseases screening. Once stored, samples could potentially be made available to global UCB banks and would therefore need to comply with international regulatory and quality standards. Quality control standards include screening units for HIV-1, Hepatitis B-virus (HBV) and Hepatitis C-virus (HCV) by individual donation nucleic acid testing (ID NAT).

(b) It is thus mandatory to have a robust, sensitive and reliable assay for detection of HIV-1 in UCB units prior to banking, to prevent the banking of potentially HIV-1-positive UCB. The commercially available Procleix®Ultrio® Plus Assay (Ultrio-Plus® assay) is used by the South African National Blood Services (SANBS) for simultaneous detection of HIV-1, HBV and HCV in donated blood. This sensitive screening test is currently performed on all blood donations received at the South African National Blood Service (SANBS) and is internationally accepted and highly successful (Crookes et al., 2007).

The assay has been validated for use in human peripheral blood and organ and cadaveric tissues, but has not yet been verified for UCB. Therefore, this study (in collaboration with the SANBS) set out to verify the Ultrio-Plus® assay for routine use in an UCB SCB for detection of HIV-1 in UCB plasma (Chapter 6).

## **1.2 Addressing the burden of high rates of HIV-1 infection in South Africa: By rendering the immune system resistant to HIV-1 infection through genetic modification of haematopoietic progenitor cells (HPCs); Background to the larger study and specific components involved in the current investigation.**

South Africa is faced with enormous challenges in the areas of HIV-1 prevention and treatment. Access to anti-retroviral clinics, compliance with drug regimens, side effects of drugs and drug-drug interactions are major problems for most South Africans living with HIV-1. Furthermore due to poor drug compliance, resistance to antiretroviral drugs is becoming a problem that cannot be solved as a limited number of antiretroviral regimens are available for salvage therapy. Multidrug resistant HIV-1 will force us to explore new therapy modalities such as vaccination; however, no vaccine is currently available for HIV-1 prevention although possible candidates are in various stages of development. Alternatives to vaccination and anti-viral treatments are therefore needed and stem cell therapy might hold the answer.

Working towards a cure for HIV-1, several studies have shown how haematopoietic progenitor cells (HPCs) could potentially serve as cellular vectors in a gene-therapy approach (Hütter et al., 2009a,b; Deeks and McCune, 2010). Rendering these cells resistant to HIV-1 infection would require genetic manipulation of HPCs (Liang et al, 2010). The long term objective of this larger project is thus to generate HIV-1-resistant haematopoietic stem cells (HPCs) for subsequent transplantation into patients with HIV/AIDS, in order to replace their endogenous HIV-1-infected HPCs. This would render the immune system of the recipient of these genetically modified HPCs – at least in part – resistant to HIV-1 infection. A proof of concept study has

previously been conducted (Hütter et al., 2009a) wherein allogeneic BM from a naturally HIV-1 resistant individual was transplanted into an HIV-1 positive individual and which subsequently generated HIV-1 resistance in the recipient.

Because the South African BM registry is not representative of South African demographics (more than 70% Caucasian), finding genetically matched BM samples for allogeneic transplantation of genetically manipulated HPCs for HIV-1 infected individuals could be problematic (Crookes et al., 2007; Ruff et al., 2008). Two possibilities exist to obtain genetically compatible HPCs for genetic manipulation: 1) Harvest autologous HPCs from HIV-1 infected individuals through apheresis (to overcome problems of rejection and graft versus host disease (GvHD)); or isolate CD34+ HPCs from allogeneic, genetically compatible UCB units (which will require immunosuppressive therapies to prevent rejection and GvHD).

The larger study aims to introduce genetic resistance to HIV-1 by isolating autologous CD34+ haematopoietic progenitor cells (HPCs) and transducing them with a lentiviral construct. This construct will target various aspects of HIV-1 infection (co-receptor binding, HIV-1 replication and transcription) in order to render the cells naturally resistant to HIV-1 (mimicking the Hütter study). These cells will then be re-administered to the patient for engraftment and reconstitution of haematopoiesis.

However, it is unclear whether early haematopoietic progenitors can be infected and/or are affected by HIV-1. Should primitive HPCs be susceptible to HIV-1 infection, autologous HPCs might already be infected or adversely affected and would therefore not be suitable candidates for gene therapy. Although some literature suggests that these cells are not susceptible to HIV-1 infection or replication, it is uncertain how the presence of HIV-1 might affect the haematopoietic capacity of these cells. This could potentially account for various cytopenias and haematopoietic abnormalities that are observed in HIV-1<sup>+</sup> patients. In the case where HIV-1 affects and/or infects primitive HPCs, allogeneic transplantation of genetically modified HPCs could be an alternative for treatment. Infants born to HIV-1 infected mothers might be able to receive their own genetically modified HPCs from their UCB units while adults could benefit either through pooling of genetically matched UCB units or expansion of UCB units to obtain adequate cell numbers for transplantation purposes. An abundant supply of UCB units stored in an UCB bank would be necessary to overcome the lack of currently available BM samples and to cover the vast genetic diversity of South African patients.

Therefore, components from the larger study that were investigated in this Thesis aimed to determine whether primitive CD34<sup>+</sup> HPCs isolated from UCB could be infected and/or are affected by HIV-1. The colony forming unit assay (CFU-assay) was used as a model to establish the haematopoietic capacity of HIV-1-exposed HPCs and the potential infectability of HPCs by screening CFUs for the presence of HIV-1 with the Ultrio-Plus® assay (Chapter 7).

The Thesis is written in article format, where each chapter has its own introduction, relevant literature, materials and methods, results and discussion, conclusion and references. The last chapter, Chapter 8, discusses the final conclusions drawn from results of all the chapters.

### 1.3 References:

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- Ruff P., Schlaphoff T., du Toit E., & Heyns A. 2008. The South African Bone Marrow Registry (SABMR) and allogeneic bone marrow transplantation. *The South African Medical Journal*, 98(7): pp.516-520.



# CHAPTER 2

## 2 Stem cell tourism

### 2.1 Introduction

Interest in the field of translational stem cell (SC) research has increased rapidly in the past decade, with exciting and promising research providing hope that cures for previously incurable diseases may well be attainable in the not too distant future. Much of the excitement originates from the ability of stem cells (SCs) to self-renew, replicate and to differentiate into any one of the more than 200 cell types in the body.

Various types of SCs with different potential therapeutic applications have been discovered and, although this may appear to be a relatively new phenomenon, these cells have in fact been used routinely for more than 50 years. The best understood are haematopoietic SCs, which have been successfully applied around the world in bone marrow (BM) transplantation for treatments of various conditions including malignant and non-malignant haematological disorders, immune deficiencies and certain genetic disorders. However, with new discoveries of different types of SCs and many potential novel applications, interest in regenerative and translational medicine has increased.

One consequence has been a dramatic rise globally in companies and clinics that sell stem-cell-related products or services. In addition to improvement in personal health and wellbeing, the increased interest in cellular and molecular medicine creates opportunities for employment, business development and entrepreneurship. South Africa has great potential for the development of regenerative and translational medicine involving SC therapies. Many thousands of people could potentially benefit from currently available therapies that SCs have to offer – e.g. bone marrow transplantation. In light of South Africa's current burden of disease and the potential for job creation, we certainly stand to gain substantially (individually and as an economy) from these and similar developments, possibly more so than many affluent countries. A single major concern for implementation and operation of such companies and clinics would be compliance with national and international regulatory standards – with the supposed precondition that appropriate national legislation and governance exist.

However, even though SCs harbour the promise of potential cures for many previously incurable disorders, this promise is easily exploited.

Although SCs appear to hold promise for future therapeutic applications (in addition to their current accepted applications), charlatans and con-men have started to prematurely promote bogus ‘SC cures’ for various – still incurable – diseases (Murdoch and Scott, 2010; Caplan and Levine, 2010). They often portray SCs as the ‘holy grail’ of cell therapies and have created much uncertainty and controversy in the field.

Unfortunately, many questionable SC practices occur in countries that lack governance and regulation. This has led to the phenomenon known as “stem cell tourism” (SCT); where patients travel abroad to undergo SC treatments not provided in their own countries (Lyndvall and Hyun, 2009).

### **2.1.1 Concerns of patient exploitation by medical tourism: Stem cell tourism**

SCT is ethically problematic in that it offers unproven, untrusted therapies as legitimate cures for currently incurable diseases (Master and Resnik, 2011). There exists a large discrepancy between published, peer reviewed literature and claims posted on these illegitimate clinics’ websites (Lindvall and Hyun, 2009; Murdoch and Scott; 2010). South Africa is vulnerable to exploitation with regard to SCT because of several gaps and inaccuracies in the current legislation (Pepper, 2012). The National Health Act<sup>2</sup> (NHA) was implemented on 2 May, 2005 while matters related to human tissue was classified under the Human Tissue Act<sup>3</sup> (HTA). However, many of the currently used scientific methods involved in scientific and medical practice had not been included in the HTA. Since then, Chapter 8 of the NHA (Sections 53,55,56,68,54 and 57 to 67) has been promulgated in order to deal with blood and blood products; assisted reproductive technology; cell-based therapy; transplantation; DNA and genetic services; tissue banks; and examination, allocation and disposal of human bodies and tissues (Pepper, 2012). Although Chapter 8 of the NHA provides some direction in the regulatory vacuum present, there is still important regulation that is either lacking scientific accuracy or absent in general, leaving room for potential malpractice.

With SC translation into the clinic (regulated or not) happening at a rapid pace across the world, South Africans are bound to be exposed to some form of SC treatment sooner or later. They need to be able to accurately distinguish between legitimate treatments and fraudulent practices and would therefore, at the minimum, need a trusted source of information to assist them in making decisions.

SCT has many facets that could lead to multiple pitfalls, each posing a unique combination of moral, legal, ethical and regulatory challenges. Hype over false therapeutic claims, ranging from the sublime to the miraculous, is endangering the entire field of SC therapies. Hopefully, these fraudulent practices will soon be curtailed by the implementation of strict regulatory frameworks – such as those established by the Food and Drug Administration (FDA) and the International Society for Stem Cell Research (ISSCR) (Strauss, 2010).

### **2.1.2 Mechanisms for promoting stem cell tourism**

While having the world at our fingertips can be tremendously beneficial, millions of people today are bombarded with myriad options and opinions, leading perhaps to the single most daunting challenge of the information age: learning to distinguish fact from fiction.

The Internet and social networking have empowered many people to gain access to information on a virtually unlimited number of topics. Many companies use the Internet and Web pages to bring their business directly to consumers through direct-to-consumer advertising. However, limited monitoring of content on the Internet often creates difficulties in verifying the accuracy and credibility of the information presented. This is especially true when it comes to the field of SCs and their current and possible future therapeutic applications and translation into modern healthcare.

Con men mainly operate by promoting their activities on the Internet and reach a much broader audience than was possible in a pre-World-Wide-Web era. They offer false hope, promises of cures and miracle healings and often advertise unsubstantiated claims on their Web pages. They play on the needs and desires of emotionally vulnerable patients to be cured and coax members of the public into signing up for unproven SC treatments provided in often precarious SC clinics. Many unsuspecting customers have fallen prey to these illicit elements, which have the potential to discredit the legitimacy of SC research and true current and future therapeutic applications (Lindvall and Huyn, 2009).

## **2.2 Factors that intensify stem cell tourism**

### **2.2.1 Lag in regulatory oversight**

Certain countries have more strict regulations (e.g. the USA with its Federal Drug Agency (FDA)) than others (e.g. China, Mexico, India, Costa Rica, Thailand etc.), with fewer opportunities for such scams in the former (Brown, 2012). Unfortunately, the South African National Health Act<sup>3</sup>

does not provide sufficient regulatory guidelines for the latest advances and discoveries concerning SCs (as mentioned previously), a large regulatory shortcoming that could potentially be exploited by opportunistic individuals. Furthermore, many South Africans have not heard of SCs. Those who have have mostly been exposed only in passing and have not been properly informed. This absence of regulatory oversight and unavailability of easily accessible, reliable information regarding SCs and their applications renders not only the individuals but also the country vulnerable to questionable global influences.

### **2.2.2 Lack of proper communication between scientists and the public**

A substantial gap exists between scientists and medical doctors that undertake legitimate SC research and the subsequent accurate translation of such research to patients. The media often sensationalises preliminary scientific findings, creating much hype based on half-truths – dangerous territory that is often exploited by con men (Laing, 2011). In the absence of appropriate legislation, increasing awareness of SCs and their promise in novel therapeutic applications for a wide range of disorders will undoubtedly bring with it an escalation in illegitimate SC practices.

## **2.3 The moral and scientific dilemma**

Since the first technique for isolating ESCs was introduced by James Thomson and his team at the University of Wisconsin, SC research has increased exponentially across the globe (Kaufman et al., 1999; Barclay, 2009). Discovering SCs in easily obtainable resources such as adipose tissue and peripheral blood together with less invasive isolation techniques for obtaining these cells (such as umbilical cord blood collection) has left an open invitation to many undesirable “stem cell squatters” in the field of SC research and translational medicine.

Legitimate research is being conducted, ethically approved and undergoing various registered clinical trials. Although preliminary results for some stem cell treatments – such as using HSCs to treat myocardial infarctions or ischemia – seem positive, very few clinical trials have, to date, successfully completed phase III, which would bring new therapy or treatment for yet incurable diseases to the market (Kavanagh and Kalia, 2011; Kale et al., 2003; Orlic et al., 2001). The proceedings necessary to accredit the treatment are unfortunately tedious and painstakingly slow. The translational process from science to medicine is complex and painstakingly slow. The only proven treatments involving SCs over the past 40 years include blood disorders

treated with adult SCs through bone marrow or blood SC transplantations for rare immunological and non-immunological disorders. In addition to these, some treatments have been approved for bone- and skin grafting and certain corneal diseases or injuries, using adult SCs harvested from the particular tissue (ISSCR, 2012)

What is presented on the one hand is scientists doing legitimate research while on the other are fraudster latching onto promising research by offering unproven treatments to ill, desperate but hopeful patients. With an increase in awareness of the therapeutic potential of SCs inevitably comes a surge of illegitimate opportunists. The dilemma is that research just takes too long to go through all the right channels before it can benefit patients. Patients often don't have the luxury of time to wait for these treatments to become commercially available or for potential therapies to go through regulation and accreditation. In the meantime, the numbers of con men increase and bigger numbers of desperate patients get offered the option of unproven treatments. Furthermore, patients have a right to access medical treatment and no law forbids them to undergo treatment of any nature to which they give consent. The end result is the exodus of frustrated and impatient patients, unwilling to wait for local approval of SC therapies yet willing to risk their health and livelihoods on unsubstantiated claims (Caplan and Levine, 2010).

Despite repeated warnings from acclaimed scientists against overseas clinics that offer curative SC therapies for a variety of disorders, many doctors and their patients ignore this advice and still opt for treatment (Lau et al., 2008). According to Sean Morrison, director of the University of Michigan Centre for Stem Cell Biology and treasurer of the ISSCR, many doctors are venturing into their own SC initiatives (Barclay, 2009). Whether they are compelled to get involved by the steadily increasing patient demand for various unproven forms of SC treatments – only having their patients' best interest at heart – or not is hard to decide, since many of these doctors also stand to gain commercially from the treatments.

Some doctors, however, recognise the potential of a variety of SC treatments (HSCs, MSCs) and instead of subjecting their patients to doubtful practices abroad would rather opt to treat their patients themselves, where they are more certain of the type and quality of administered SCs and the correct application of them. This not only places them in a moral and ethical dilemma but could also have serious consequences for their licences as practitioners if they perform unlicensed and ethically unapproved procedures.

It is important to note that not all doctors who offer SC treatments are imposters. Just the same, as Timothy Caulfield at the University of Alberta's Health Law Institute, Edmonton, Canada states, people that offer treatments should publish their data in scientific, peer-reviewed journals (Barclay, 2009). The substantial risks involved in uncontrolled treatments necessitate verification of purported results in a controlled environment through appropriately structured clinical trials (Cyranoski, 2009). These should include assessments of safety, efficacy, harvesting, storing/culturing of cell isolates, dosing, administration procedures and ethically approved information leaflets and informed consent forms (Lindvall and Huyn, 2009). This transparency gives other researchers the opportunity to verify the claims, safety and efficacy of the treatment.

### 2.3.1 Emerging stem cell clinics and treatments

The number of clinics that offer SC treatments has increased exponentially in the past four years. In 2009 there were an estimated 200 clinics and, although it is difficult to determine an exact number because of the often clandestine nature of their activities, it is thought that the current estimate well exceeds this number (Cyranoski, 2009) and that they are found in various countries, as illustrated in Figure 1. Places such as China, Mexico, India, Costa Rica, Russia, Thailand, Germany, Hungary, Korea, the Dominican Republic, Jordan, Kazakhstan and Barbados are popular destinations, since regulations are generally less strict or non-existent (Caplan & Levine, 2010).

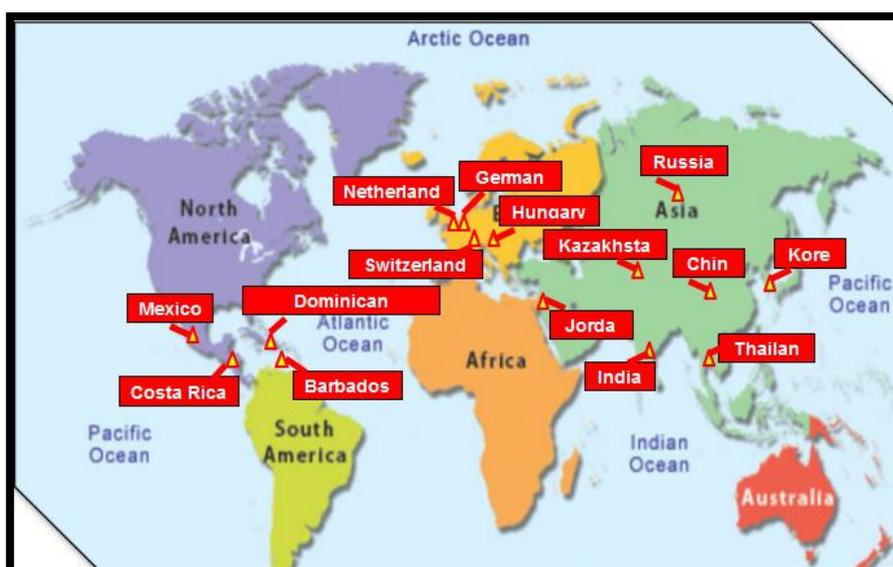


Figure 1: Known areas where illegitimate stem cell clinics are emerging around the World.

Some of these clinics offer treatments and cures for still incurable disorders, including amyotrophic lateral sclerosis (ALS), spinal cord injury, stroke, multiple sclerosis (MS), Parkinson's disease, all forms of blindness including optic nerve damage, systemic lupus erythematosus, brain injury, cerebral palsy, Down's syndrome, Alzheimer's disease, heart disease, diabetes and autism. Of the less serious treatments, cosmetic enhancement is at the top of the list with anti-aging creams, fibroblast/collagen injections (as an alternative to botox) or general 'health enhancements' (Lau et al., 2008).

Of particular concern are the cell sources. According to a study carried out by Lau *et al.* (2008), it was found that cells harvested from adult autologous SCs were provided in nine sites, comprising 47% of their study cohort. Bone marrow comprised 37% (in seven sites) of autologous cells used while cells were also obtained from adipose tissue and blood donations. The other 53% of cells were from sources such as foetal SCs, cord blood SCs, and embryonic SCs, peripheral blood, patient fat (adipose tissue), aborted foetuses, patient's skin, animal tissues, and human placental tissue. Treatments were provided for a wide variety of disorders ranging from neurologic and cardiovascular diseases to allergies. These were generally treated by SC infusion into cerebrospinal fluid (six sites; 32%) (lumbar puncture) while IV infusion was also common (Lau et al., 2008).

In addition to obvious health and safety risks, these clinics often charge patients exorbitant amounts averaging from \$15 000 to \$25 000 USD for their SC treatments. Costs are often unsubstantiated and do not include patient travel or accommodation (Cyranoski, 2009).

### **2.3.2 Advocates for stem cell tourism**

Advocates for SC treatments do not necessarily endorse SCT, but their fervour to provide treatment often clashes with opponents of SCT.

People who advocate a patient's right to access all forms of treatment, potential or real, present the following arguments to support their case:

1. Patients often don't have the luxury of time. Their diseases usually progress fast and alternative SC treatments (proven or unproven) are their last option.
2. Clinical trials are costly and finding appropriate funding for trials is challenging (Barclay, 2009). In addition, clinical trials prolong the time until treatments become acceptable and therefore available to patients.

3. Advocates propose that they have patients' best interest at heart. They work with dying patients daily and they claim, consequently, to not have time to perform studies or write articles that are subjected to peer review.
4. They claim that SC treatments have thus far yielded little or no adverse effects (citing no graft- versus host-disease (GvHD) rejection of cells from autologous donors)
5. They disagree with the FDA with regard to classification of treatments with autologous cells. The FDA classifies all cells that are not minimally manipulated as 'drugs' that need to adhere to FDA rules and regulations pertinent to administration of a 'drug'. Conversely, advocates for SC treatments maintain that a body's own cells are not drugs and should be exempt from FDA regulatory requirements. Advocates accuse the FDA of stalling developments in SC treatment since they do not stand to gain directly from emerging SC treatments and potentially stand to lose profit because of a shift in medical treatment from pharmaceutical drugs to cell therapy. A recent example is the case of the FDA against the Broomfield, Colorado, Clinic, Regenerative Sciences. On 25 July, 2012 the US district court in Washington DC ruled in favour of the FDA's injunction (made in 2010) against Regenerative Sciences. They had been treating orthopaedic problems with their Regenexx® product, which the FDA classifies as a drug since cells were not minimally manipulated. However, Regenerative Sciences' medical director, Dr. Christopher Centeno plans to appeal the court's decision and maintains their product is not a drug (Aldhous, 2012)
6. Advocates want to capitalise on the favourable climate for new business start-ups in SC treatments. They are afraid of missing the opportunity provided in the emerging market.
7. Some advocates are furthermore driven by the potential fame and recognition of potentially curing a previously incurable disease with their SC treatments. They see themselves as pioneers and argue that technology always precedes regulation.

### **2.3.3 Adversaries of stem cell tourism**

Adversaries – opponents to unproven SC treatments – are cautiously optimistic about the potential promises provided by SC treatments. They do not oppose the development of SC treatments, but rather propose a safe and regulated environment in which to practise and develop new treatments.

The case against SCT centres on the following points:

1. There should always be balance in new developing fields. Emphasis on scientific progress cannot override a scientist's responsibility towards the public to ensure safe and reliable treatments. Harmony should always exist between risk and benefit that should be obtained through phased and structured assessment of safety, efficacy, dosing and administration of treatments. Informed consent procedures must be assessed and approved and all innovation outside of research must be demonstrable, scientific and clinical (Cyranski, 2009).
2. Opponents object to unrealistic, incomplete and false marketing often associated with unproven SC treatments that are made available to the public. Advertisements are generally over optimistic or positive, understating potential risks involved, and have numerous unsubstantiated claims of treatment efficacy without the necessary scientific proof to back up the claims (Master and Resnik, 2011; Caplan and Levine, 2010).
3. Adversaries object to the lack of transparency from companies providing SC treatments. At best, selective information is made available to patients and the public, creating opportunities for exploitation (Lau et al., 2008). Furthermore, little or no information is provided on experimental protocols, procedures or controls that allow for an independent analysis of the claims (Cyranski, 2005).
4. It is imperative to subject all work to objective, peer-reviewed assessment, proper regulatory oversight and to conform to requirements from ethical councils (Lau et al., 2008). Patients are generally not followed up after treatments and there are no records kept of potential side effects. Without these measures, it is impossible to know the lasting effects of treatment, whether potential improvements are due to placebo effects or whether they are only temporary, and whether there are any side effects related to the cells administered or their route of harvesting or administration. This information is vital to the entire scientific community and could aid in developing effective, lasting treatments. With a lack of FDA-approved clinical trial data, 'evidence' is anecdotal and controversial at best.
5. Opponents of SC tourism maintain that false claims of safety and efficacy of treatments will eventually jeopardise legitimate SC research and its clinical translation. Once public confidence in these treatments is shaken, it will be difficult to convince people otherwise.
6. Another concerning factor is the lack of understanding by providers of SC treatment of the underlying biology of many of the disorders and their proposed SC treatments (Barclay,

2009). The fate of injected cells is not well understood and could lead to serious side effects or even death.

7. Erroneous therapeutic misconceptions abound and have been turned into lucrative business models (Cyranoski, 2005). Furthermore, there are no cost regulations for any of the provided treatments and patients are vulnerable to financial exploitation.

## **2.4 How to curb stem cell tourism?**

Legitimate SC entities could curb malpractice and corruption through transparency, peer review, clinical trials, by addressing current misconceptions with regard to SC therapy and by raising public awareness of current clinical applications and exploitations of SC treatments (Lindvall and Huyn, 2009).

This calls for better governance of genuine research and open and accurate communication from scientists to the public. Creating an overarching, global, independent regulatory body could be one way in which to curb the wealth of inaccurate information and criminal activities on the Internet. This regulatory body could serve as a platform for translating legitimate research through open communication with the global public. In turn, each country should have its own regulatory body preferably linked to the global governing body. The regulatory bodies must follow up on and monitor all therapeutic claims. They should actively raise public awareness of current SC therapies and provide an accurate and clear consumer's guide to approved uses for cell therapies.

By enabling legitimate SC practices to operate under proper legislation and simultaneously increasing awareness of these legitimate practices, one could potentially reduce the appeal offered by illegitimate practices.

All doctors, scientists and suppliers of SC treatments must adhere to the minimal ethical, scientific and medical standards for treating patients with any therapy. Because many clinics fail to do so, the ISSCR has put together a task force and posted these minimal standards, together with a list of guidelines and clinic requirements, on its website ([www.isscr.org](http://www.isscr.org)) (ISSCR, 2012). This includes a list of questions about the treatments offered that patients could ask the specific clinics and that ought to be answered. Through this effort, the ISSCR aims at publishing a list of clinics that it believes adhere to the minimal standards of operation as suggested by the task force (Taylor et al., 2010). The ISSCR patient handbook could also be used both by patients

seeking treatment abroad and their physicians to make informed decisions about SC treatment and the necessary questions to ask the treatment providers prior to signing up for treatments (ISSCR, 2012) (<http://www.closerlookatstemcells.org>).

A similar approach has been taken by the International Cellular Medicine Society (ICMS). The ICMS has realised that there is virtually no stopping patients from going for so-called SC treatments and has therefore opted to encourage doctors and clinics to treat their patients on the basis of ICMS guidelines, which can be found on its website.

Caplan and Levine (2010) have mentioned how the neglect from mainstream medicine to act decisively on the issue of quackery has aggravated the problem, leading to whole countries purposefully gearing themselves to capitalise even more on the steady inflow of patients from abroad.

## 2.5 Conclusion

The vibrant field of SC research and treatment consists of dramatically different stakeholders, all of whom have specific interests and agendas. For all parties involved, the stakes are high and understanding the dangers of SCT is imperative. It should be pointed out that the use of the word “tourism” has arisen from the propensity for patients to travel long distances to receive treatments in foreign countries. However, the principles outlined above are equally applicable to activities that may exist in one’s own country.

In order to reap the greatest benefit from what SCs have to offer, it is imperative to understand the current SC milieu. It is necessary to find the balance between scientific soundness in new discoveries and medical innovations and uncontrolled, experimental treatments that abuse the current regulatory vacuum. The focus should be on the creation of safe, effective, scientifically sound treatments in a controlled regulatory environment without compromising patient health care. These therapies should furthermore offer patients greater than or at least equal benefit to what conventional available therapies can provide. Unless the therapy provides benefit to the patient, it will be unethical and thus unacceptable to administer (Lindvall and Huyn, 2009).

Caplan and Levine (2010) succinctly summarise the problem:

*Those who are drawn to SC therapies are often confused about the innovative status of these interventions, overly reliant on unsubstantiated claims about the quality of biological material being administered, or unable to readily locate balanced assessments of what medical tourism may have to offer for their particular problem. Professional societies and mainstream SC researchers have an obligation to do more.*

In light of these considerations, South Africa is especially vulnerable. With SC research still in its infancy in South Africa, we still have a clean slate to write on. As researchers we are in a position to do more for our country and its people.

The global atmosphere around SC treatments underscores the importance of distinguishing legitimate research and therapeutic application from potential fraudulent practices. As any virus spreads, so too will the infection of SCT, in this way rendering South Africa vulnerable to elements that could taint emerging SC research in SA.

One manner in which to further legitimate SC practices in South Africa is by establishing a reliable and easily accessible source of information. This information should be freely

accessible to the public, provide reliable information on SC donations and therapeutic applications and in this way establish safe and legitimate avenues for regulated SC therapies that will allow patients to distinguish legitimate SC therapies from fraudulent practices. A public umbilical cord blood stem cell bank could be a first trusted and publicly accessible entity to provide and distribute the correct information pertaining to legitimate SC therapies in South Africa.

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