SURE Rapid Response

What is the role of **stem cell therapy** in the management of **non-communicable diseases?** How does it work and what are its implications on the health system?

August 2011

This rapid response was prepared by the Uganda country node of the Regional East African Community Health (REACH) Policy Initiative.

Key Messages

- Stem cell therapy has the potential to improve clinical outcomes of chronic diseases: there is consistent improvement in myocardial function combined with safety from studies using autologous bone marrow stem cell transplantation in myocardial infarction
- Stem cell therapy also has the potential of improving social and economic aspects of households affected by chronic degenerative diseases.
- Translating stem cell research into policy and practice is faced with a number of barriers including ethical, financial, human resource, time, political and legislative.

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SURE
Supporting the Use of Research Evidence

REACH
Regional East African Community Health Policy Initiative

EVIPNet
EVIDENCE-INFORMED POLICY NETWORK

Who requested this rapid response?

This document was prepared in response to a specific question from a Senior Health policymaker in the MOH Uganda.

! This rapid response includes:

- **Summary of research findings,** based on one or more documents on this topic
- **Relevance** for low and middle income countries

X Not included:

- Recommendations
- Cost assessments
- Results from qualitative studies
- Examples or detailed descriptions of implementation

What is the SURE Rapid Response Service?

SURE Rapid Responses address the needs of policymakers and managers for research evidence that has been appraised and contextualised in a matter of hours or days, if it is going to be of value to them. The Responses address questions about arrangements for organising, financing and governing health systems, and strategies for implementing changes.

What is SURE?

SURE – Supporting the Use of Research Evidence (SURE) for policy in African health systems - is a collaborative project that builds on and supports the Evidence-Informed Policy Network **(EVIPNet) in** Africa and the Regional East African Community Health **(REACH)** Policy Initiative (see back page). SURE is funded by the European Commission's 7th Framework Programme.
www.evipnet.org/sure

Glossary

of terms used in this report:
www.evipnet.org/sure/rr/glossary

Background

The World Health Organization (WHO) in its World Health Statistics report of 2008 pointed out that the global burden of disease was fast moving away from infectious diseases to non-communicable diseases, with chronic conditions being the current leading causes of death globally (1). The same report predicted that the shifting health trends mean that leading infectious diseases like HIV, tuberculosis, malaria, diarrhoea and neonatal infections will become less significant causes of death globally over the next 20 years. In developing countries, it is predicted that by 2020 NCDs will account for seven out of every 10 deaths in developing countries (2). The table below shows the shifting epidemiological trends in the developing countries.

How this Response was prepared

After clarifying the question being asked, we searched for systematic reviews, local or national evidence from Uganda, and other relevant research on the topic. The methods used by the SURE Rapid Response Service to find, select and assess research evidence are described here:

www.evipnet.org/sure/rr/methods

Evolution of NCDs in developing countries (in million)

	Non-Communicable Diseases	Communicable Diseases (incl. maternal, perinatal, nutritional)	Injuries	Total
1990	18.7 (47%)	16.6 (42%)	4.2 (11%)	39.5 (100%)
2000	25.0 (56%)	14.6 (33%)	5.0 (11%)	45.0 (100%)
2020	36.6 (69%)	09.0 (17%)	7.4 (14%)	53.0 (100%)

Being able to take care of such a growing threat is of interest not only to clinicians but to managers and policy makers too. Many of these degenerative diseases cause irreversible damage to the body, disabling the patient over and for a long period of time. In addition to preventative measures efforts are geared towards finding curative interventions. One of the promising (but still being researched) intervention is cell-based therapy.

Cell-based therapy also commonly known as regenerative medicine is a fairly new phenomenon with the potential to repair or replace diseased tissue or organ function lost due to damage, or even congenital defects (3). Commercial products based on cell therapy are already available in the developed countries for skin ulcers and sports injury like injury to the knee cartilage, however a multitude of research is going on to establish the benefits and safety of use of this therapeutic method in treating several chronic degenerative diseases including cardiac, renal conditions, diabetes among others.

The idea of using stem cells as therapy was first considered in 1960 when the capability of bone marrow stem cells to reconstitute hematopoeisis in mice was discovered (4). Later the idea was extended to the formation of vascular elements from bone-marrow derived endothelial progenitor cells. This although controversial at first has in fact been increasingly embraced by both advocates and opponents alike. Stem cell therapy stimulates interest because it challenges the old notion that organs and tissue like heart muscle cannot be repaired once necrosis has occurred from coronary occlusion, indicating an irreversible damage. Stem cell therapy has generated the hope that in fact regeneration may be possible in cardiac, neural, pancreatic and other tissue. This has already been shown in pre-clinical studies carried out in animal models.

Facts or questions that a clinician and decision maker would be interested in when considering stem cell research include:

- What kinds of diseases could and should be treated using this therapy?
- At what point in the disease is the treatment helpful?
- Which particular cells should be injected?
- How should the cells be delivered?
- What are the mechanisms by which the transplanted cells exert influence if at all they do?

This paper will look at the research evidence available on the area of stem cell therapy in the management of non-communicable diseases. It will consider the above questions but also look at the implications stem cell research has for the health system and the issues surrounding its translation into policy and practice.

Summary of findings

It was thought that the heart does not regenerate because adult cardiomyocytes (cells that form the heart muscle) do not have this capacity once formed at conception, and that the only response to an increased functional demand is hypertrophy. However evidence is now emerging that in fact cells regenerating the heart exist and may be coming from bone marrow as is seen in bone marrow transplant patients who undergo a myocardial biopsy (5). The same has been seen in kidneys of mice after they receive a bone marrow transplant. However, apparently this regeneration is to a degree that has no clinical benefit.

Furthermore, studies have shown that the plasticity of adult stem or progenitor cells (more differentiated stem cells) that have been released from the bone marrow is much larger than has been previously

known, that is, that stem cells were committed to specific cell lines and that with increasing maturity they would lose their ability to differentiate or return to an immature state or to transdifferentiate changing to another cell line (6).

The cells of human origin could be somatic (autologous or allergenic), adult stem cells or embryo-derived stem cells or stem cells from umbilical cord blood.
There are a few reports on somatic cell therapy trials, but this is generally used in cancer vaccinations as dendritic cells (7).
Adult Stem Cells (ASCs) which have the capacity of self-renewal and differentiation into adult cell types hold promise for many chronic degenerative diseases like neurological disorders, cancer, cardiovascular diseases and diabetes. Although a challenging task, identification and isolation of these rare cells has been done from different tissues such as adipose tissue, pancreas and liver, as well as from umbilical cord blood and bone marrow. Stem cells isolated from adult bone marrow have the potential to differentiate into different cell types, and in fact bone marrow transplantation (BMT) is an approved cell-based life-saving treatment for many incurable diseases.
Umbilical cord blood is a rich source of stem cells. The stem cells show multi-lineage differentiation potential and differentiate into adipogenic, chondrogenic, osteogenic and neuronal lineages when cultured with lineage-specific differentiation medium, thus making it a good source for regenerative medicine.
Human embryonic stem cell (hESC) has established itself as a valuable tool to study development. However it is also a potential source of stem cells for regenerative medicine. Their use in cell replacement therapy is being debated due to numerous ethical and safety issues (7).
Several cell types have been experimented on in a bid to establish their usefulness in heart regeneration but of these autologous bone marrow cells or circulating progenitor cells have so far been found to have potential usefulness. There is more data on these and skeletal myoblasts than any other types (8).

Theory of how it works : The genetic and cellular mechanisms that initiate trans-differentiation of stem cells are still poorly understood, but it is increasingly being shown that transplanted stem cells undergo a "homing" process in which they are attached to the site of injury (8). The cell have been shown to increase the functional recovery of the affected organ after ischemia by physically forming new blood vessels, differentiating to the local myocytes and—additionally or alternatively—by providing proangiogenic and antiapoptotic factors promoting tissue repair in a paracrine manner (9).

Efficacy and Effectiveness

The first clinical trial on this subject was carried out by Strauer et al in 2002 and this was on patients with acute myocardial infarction who received progenitor cells from the bone marrow. The results showed that transplanted autologous BMCs may lead to repair of infarcted tissue when applied during the immediate post-infarction period (10). The results also showed that the intracoronary approach of BMC transplantation seems to represent a novel and effective therapeutic procedure for concentrating and/or depositing infused cells within the region of interest. The alternative is to give them using the intravenous route but with this, only a very small fraction of infused cells can reach the infarcted region. The same study also noted that cell transplantation within the first 5 days after acute infarction is not possible for logistical reasons and is not advisable because of the inflammatory process. On the other hand, transplantation 2 weeks after infarction scar formation seems to reduce the benefit of cell transplantation. Although the ideal time point for transplantation remains to be defined, this study concluded that it is most likely between days 7 and 14 after the onset of MI.

A literature review followed by a pooled subgroup analysis of randomized controlled trials was done to assess the impact of timing on efficacy and safety of intracoronary autologous bone marrow stem cells transplantation in acute myocardial infarction (11). It concluded that bone marrow stem cell transfer at 4 to 7 days post-acute myocardial infarction was superior to that within 24 hours in improving left ventricular ejection function, decreasing Left ventricular end-systolic dimensions, and reducing the incidence of revascularization.

In a pilot of a clinical trial pilot done to investigate among other things, the initial clinical outcome of intracoronary infusion of autologous progenitor cells in patients with acute myocardial infarction, the intracoronary infusion was associated with a significant increase in global left ventricular ejection fraction, a profound improvement in wall motion abnormalities in the infarct area, and a significant reduction in end-systolic left ventricular volumes 4 months after the infarction occurred, suggesting a beneficial effect on post-infarction remodelling processes (12). The improved left ventricular function was accompanied by complete normalization of coronary flow reserve in the infarct artery and by significant increases in myocardial viability within the infarcted segments.

In a systematic review and meta-analysis of available prospective randomized controlled trials (RCTs) to analyze the efficacy and safety of BMC treatment with global left ventricular function in acute myocardial infarction found, several studies revealed a significant improvement of left ventricular ejection function, but others found no difference of between the group receiving bone marrow cell therapy and that not receiving (13). The discrepancies could have arisen from some studies having very small sample sizes, some therapy being combined with other interventions, different techniques of handling of the infused cells, different times of initiation of treatment, and others.

A double-blind, placebo-controlled multicentre clinical trial involving 204 patients, done to investigate the clinical outcome after intracoronary administration of autologous progenitor cells in patients with, concluded that there was associated significant reduction of the occurrence of major adverse cardiovascular events after acute myocardial infarction.
Several other studies had conclusions similar to the ones referred to here (14-17). However they all noted that there was a need for larger-scale studies.

Safety issues

The most consistent improvement in myocardial function combined with safety has come from studies using autologous bone marrow stem cell transplantation in myocardial infarction (8). Furthermore, the intracoronary approach has been identified as one of the safest, the most feasible and minimally invasive method for cell transplantation.
In a study whose primary aim was to examine whether intracoronary injection of autologous mononuclear bone marrow cells resulted in an improvement in global left ventricular function, all of the procedures on the subjects were well tolerated and no inflammatory reaction or abscess was detected at the site of iliac puncture after the bone marrow harvesting procedure (18). In this same study the invasive coronary catheterization was associated with some mild angina during the balloon inflations for the cell infusions but there were no procedural complications during cardiac catheterization related to intracoronary progenitor cell injections. Furthermore, cell transfer did not increase the risk of adverse clinical events, tumor occurrences, in-stent restenosis, or life-threatening arrhythmic events.
In another study, a phase I clinical trial done in Brazil to test for the safety and feasibility of cell therapy using bone marrow mononuclear cells (BMMC) in idiopathic dilated cardiomyopathy, it was found that intracoronary delivery of autologous mononuclear cells from bone marrow is safe and feasible in the idiopathic dilated cardiac setting (19).
Another study done to assess the feasibility, safety, and efficacy of a combination of high-dose chemotherapy and autologous hematopoietic stem cell transplantation in patients with severe, refractory rheumatoid arthritis (RA) found that these given in succession are feasible and safe, and can result in long-term improvement of disease activity in patients whose condition previously did not respond to conventional anti-rheumatic drugs or TNF blocking agents (20).
However one controlled study (had a comparison group) done to test the feasibility, safety, and functional effects of the use of enriched progenitor cells after intracoronary administration in patients with recent myocardial infarction found that although feasible and associated with improved left ventricular performance paralleled with increased myocardial perfusion and viability, there was increased incidenc-

es of coronary events (21). This however contradicts results from a similar controlled study done two years later, in which intracoronary infusion of selected progenitor cells to a previously infarcted and nonviable anterior wall was found to be safe (22).

Implications to the health system

Clinical: stem cell therapy has the potential of improving the management of degenerative diseases and their chronic characteristics. Aside from the benefits to the patients in terms of organ function like improved heart function, there are less visits or reduced stay in the hospital. Furthermore there are less complications leading to rehabilitative treatment. Therefore the burden on the hospitals is less in terms of the expense of management of the disease, its duration, the complications requiring prolonged treatment and care, and congestion. There is potential anticipated for the treatment of the following diseases which incidentally are some of those whose management has still been a challenge for the clinicians: cancer, Type 1 diabetes mellitus, Parkinson's disease, Huntington's disease, Celiac Disease, cardiac failure, muscle damage and neurological disorders, among many.

Economic: the financial implications on individuals, households and nations on the treatment of chronic diseases are enormous, in both direct and indirect costs. Taking an example of a disease like diabetes, in the low income countries, patients and their families bear almost the whole cost of the medical care they need. In Mozambique, diabetes care for one person requires 75% of the per capita income while in Mali it amounts to 61% and in Zambia 21% (23). The World Health Organization (WHO) predicted net losses in national income from diabetes and cardiovascular disease of about 336.6 billion international dollars in India, 49.2 billion international dollars in Brazil and 2.5 billion international dollars in Tanzania between 2005 and 2015. In Sudan costs on diabetic children and adults represented up to 23% of family incomes (24). Besides excess healthcare expenditure, diabetes also imposes large economic burdens in the form of lost productivity and foregone economic growth. The largest economic burden is the monetary value associated with disability and loss of life as a result of the disease itself and its related complications. The same can be said for all other chronic diseases, the financial and economic losses are high.

However stem cell therapy is still an expensive venture too. It is hardly taken care of by governments at the moment and so individuals have to meet all direct and indirect costs. A single treatment involving four injections of stem cells may cost up to 24000 euro (25). But most of these are also still parts of research. It is hoped that when the research is done this cost will come down significantly and would be relatively low in comparison to the lifetime treatment that one would have needed without it.

Social: The debilitating nature of these diseases reducing one's ability to lead a normal self sufficient life but waste away slowly is one that reduces the quality of life. Stem cell therapy has the potential of reversing or reducing this. There is however an ethical debate on the source of cells, especially referring to the destruction of embryos at day 5-7 after fertilization at the blastocyst stage and therefore the moral status of the embryo. The debate centers around use of embryos that have a right to life and also the fact that they would have died or been destroyed anyway if they are part of in-vitro fertilization. There has had to be enaction of laws to guide the work but the debate is still active in the public.

Barriers of translation of stem cell research to action or policy (26)

- Political: there is a lot of debate raised especially by the media when they report new claims as soon as or even before they appear in the scientific literature or are presented at scientific meetings. These are then discussed extensively with media hosts presenting their views and encouraging the public to do so as well. The politicians are then forced to give their view too but usually under different pressures from those for and against the issue proposing policy initiatives in the process. This is what has been the case with stem cell research. This high level of media and public interest increases scrutiny and demand for accountability. Although accountability is to be expected, onerous scrutiny and regulatory requirements may in fact prove counterproductive.
- Ethical: The most common argument is against human embryonic stem cell research and the controversy usually arises from the fact that it involves the destruction of human life, which, according to opponents, begins at conception. Furthermore opponents argue that human embryonic stem cell research is unnecessary because adult stem cells (ASCs) have the same therapeutic potential as human embryonic stem cells but advocates of human embryonic stem cell research counter this and say that adult stem cells will never be pluripotent or sufficiently able to expand into stable cell lines, which are required for both basic and applied research to develop cures against a range of devastating illnesses, such as Alzheimer and Parkinson diseases, or to repair spinal cord injuries.
- Legislative: the formulation of public policy on stem cell research like any other policy usually competes for attention with a multitude of other issues like climate change and terrorism in governments that are involved in this research. In cases where decisions and policies on issues for which policymakers do not have the time or inclination to do the necessary research to inform their decisions they tend to use emotions or cognitive basis to decide. Regulations enacted in haste and in such an environment usually reflect poor understanding of the subject at hand and may prove to be a barrier.
- Financial: stem cell research is still a very expensive venture. This coupled with its controversial issues finds it hard to attract private funding or investment. It is quite costly to develop a new therapy

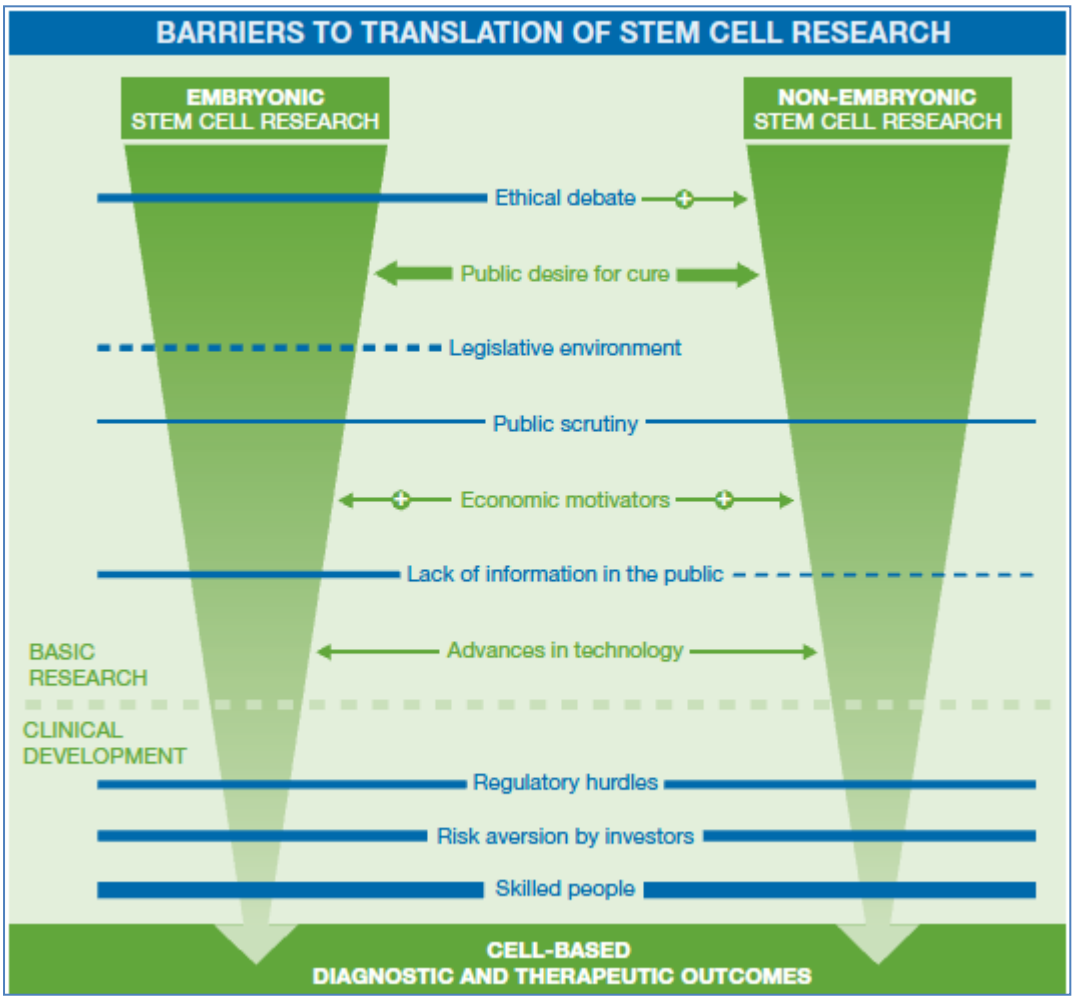
from basic research through development, regulatory approval and clinical trials. These investments are often covered initially by the venture capital sector, and subsequently by the biotechnology and pharmaceutical sector. However, investors have so far been reluctant to make such investments into cellular therapies for a number of reasons:

i. there is skepticism about the likely success of stem-cell research, on the basis of the historical experience of the hyperbole surrounding gene therapy
ii. some companies are sensitive to the public debate and are unwilling to perform or support hESC-based research, in part to avoid damaging their brand name
iii. there is uncertainty about whether the technology will produce defendable and exploitable intellectual property
iv. there are regulatory questions that cannot yet be answered because the field is still developing. For example, how would drug approval agencies regulate a therapy that involves cells, medical devices and biochemical factors?
v. Probably the largest barrier from an investor's point of view, are doubts about whether a marketable product can be defined. Much of the rhetoric implies that some cell types will be used therapeutically. But what will the product be? Will it be the cell or the way in which the cell is isolated, expanded or delivered? What else will be necessary for a therapeutic product?
vi. the most economically successful products are those that can be widely distributed and do not require individualization for each patient. Despite the alleged advantages of generating autologous cells from ASCs, such treatments would undoubtedly be less economically feasible.

- Human resources: one wonders why there has been such little progress despite the fact that it is legal to do stem cell research even on embryonic stem cells in countries like the UK, South Korea and Israel. This may be partly explained by the lack of human resource. This research involves or uses elite skill. It is less than a decade since the first derivation of a hESC line and the manipulation of these cells and their environment is a highly skilled art that few scientists have yet mastered. A major limitation on the field of stem cell research is, therefore, a shortage of human research skill that can only be overcome slowly.
- Time: it took 35 years of research into haematopoietic stem cells to decide whether an adult cell is a stem cell. Each new potential adult stem cell source will need to be similarly assessed for self-renewal, long-term genetic stability, multipotentiality and potential to regenerate its own organ of

origin. This in turn will require the development of new and unique assays specific to that cell or organ. This is likely to take a number of years and so progress in this field will take time.

The diagram below is a schematic representation of the barriers that translating stem cell research into policy is bound to face. These are issues that policymakers should pay attention to.



Source: Melissa Little, et al, 2006.

Conclusions

Stem cell research is a fairly novel but potential therapeutic method that could easy on the burden of non-communicable diseases if translated into practice. There is a lot that is still not known about it but preliminary and current pre- and clinical research has shown that it is efficacious, feasible and safe. Stem cell research is potentially beneficial clinically, economically and socially to any population but is however still facing several barriers ethically, financially and in human resources among others.

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Conflicts of interest

None known.

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