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Opinion paper

Stem cell therapy: facts and fiction

C. Spits

Research Group Reproduction and Genetics, Vrije Universiteit Brussel, Laarbeeklaan 101, 1090, Jette.

Correspondence at: Tel.: +32(0)24774635; e-mail: Claudia.Spits@vub.ac.be

Abstract

This opinion paper is a brief overview of the current state of the translation of stem cell therapy from the bench to the clinic. The hype generated by the great medical potential of stem cells has lead to hundreds of clinics worldwide claiming to have the cure for every imaginable condition. This fraudulent practice is far from the reality of scientists and bona fide companies. Much effort is put into addressing all the hurdles we have been encountering for the safe use of stem cells in therapy. By now, a significant number of clinical trials are booking very exciting progress, opening a realistic path to the use of these amazing cells in regenerative medicine.

Key words: **Embryonic stem cells, induced pluripotent stem cells, stem cell therapy, clinical trial, regenerative medicine, safety.**

If you open your web browser and type 'stem cell therapy' into your search engine, you will get over 18 million results in the blink of an eye. Strikingly, the vast majority of the top hits, including the advertisements on the side of your page, are from companies and hospitals offering stem cell therapy to treat virtually any condition. Take for instance the clinic of Prof. Smikodub (http://cell-treatment.com). They promise a cure for diabetes, anemia and cirrhosis, but also, brace yourself, for fading potency (yes, sexual problems), sterility, cancer and HIV. And, who is Prof. Smikodub? You would expect an eminency in stem cell research to be leading such a revolutionary healthcare programme. Well, Pubmed yields exactly seven papers for Prof. Smikodub, all of them in russian, two of them on the use of hematopoietic stem cells to treat cancer (a fascinating idea if you ask me). The truth is that Mr. Smikodub, and all of the others offering the miracle cure to literally any of our problems, are a fraud. Sadly, clinics such as Mr. Smikodub's have been popping out of the ground like mushrooms, and not only in fishy looking places such as the red-light district of Moscow. Celltex Therapeutics is based in Houston, Texas, and has been subject of much controversy because of questionable practices, and is now being thoroughly grilled (and hopefully closed) by the US Food and Drug Administration (www.biopoliticaltimes.org/article.php?id=6284; www.nature.com/news/stem-cell-therapy-takes-off-in-texas-1.10133). Another example comes from XCell-Center in Dusseldorf, that exploited a loophole in the German law to charge up to 25.000 € for experimental procedures. The clinic has now been closed after the death of an 18-month old child after a stem cell infusion in the brain (www.msrc.co.uk/index.cfm/ fuseaction/show/pageid/1831).

One of the hints that a clinic may be a scam is that they offer treatments for a large variety of conditions using one and the same type of stem cell, mostly isolated from a part of the body that is different to the part being treated. There are many different types of stem cells, including embryonic stem cells and adult stem cells. Whilst embryonic stem cells originate from the earliest stage of development, adult stem cells can be found in most (if not all) of the tissues of the body. Adult stem cells differ from embryonic stem cells in that they will only spontaneously generate cells from the same lineage as they are. For instance, hematopoietic stem cells can generate blood, neural stem cells can produce neurons, but neural stem cells will not make blood. It is therefore critical that the type of stem cells is appropriate for the treated disease. Conversely, embryonic stem cells could be theoretically used to obtain cells of all lineages, as they are much more primitive than adult

stem cells, and retain the embryonic ability to form a complete individual. Finally, there are induced pluripotent stem cells, the most exciting Japanese export since the Tamagochi. These cells were first described by Takahashi and Yamanaka in 2006, and since then have boomed in the world of stem cell research. They basically are terminally differentiated adult cells that have been send back to their embryonic state by inducing the overexpression of a few genes. These genes are able to switch on the pluripotent capacity of the cell, making it now possible to generate embryonic stem cell-like cells from virtually any cell from any person.

Disappointingly, we are still facing several important problems in the translation of any of these cell types from the bench to the clinic.

On one hand, we have practical problems related to the way stem cells are cultured, and particularly embryonic and induced pluripotent stem cells. Currently, although much effort is spend into developing clinical grade culture systems, most of the embryonic stem cell lines are still grown in contact with xenogenic products and cells. Another bottleneck that is more difficult to solve is that human stem cells can hardly be bulk cultured. To be able to effectively treat a patient, a large number of cells are needed, and with the current culture methods this is, to put it mildly, challenging.

The differentiation protocols are another important point of attention. For a differentiation protocol to be useful in a clinical setting, it has to be able to efficiently induce the differentiation of the stem cells into a specific cell type. The protocol should yield only the specific target cell, the differentiation should be terminal (i.e. the cells should not be able to revert to a pluripotent state) and there should be no undifferentiated cells left. If a protocol to differentiate to insulin producing beta cells also yields muscles, neurons, and a plethora of other cells, it is not suitable to inject it into a patient's pancreas. And, importantly, if there are still pluripotent cells in the culture, these cells may have the ability of forming tumours in the recipient. It is a sad fact that many of the published papers on differentiation protocols exaggerate their results and prove very hard to reproduce in other laboratories.

The sources of the embryos used to derive the ESC lines, and the stem cells themselves (of any kind) are still very poorly characterized. Much work is still to be done to reach a consensus on which are the necessary tests to ensure that a line is safe to use. One of the points that are currently receiving most attention in this sense is the genomic instability embryonic and induced pluripotent stem cells display. Many of the abnormalities these cells carry are very reminiscent of those acquired by cancer cells. It is therefore important to evaluate if these abnormalities decrease the capacity of mutant stem cells to terminally differentiate and increase the risk of generating (malignant) tumours.

One of the problems of testing the ability of stem cells to form tumours is that all work done for human stem cells is carried out in mice. Although it is obviously the best we can do, the mouse is not the natural environment of human cells, and it may well be that human cells just grow better in a human environment. Therefore, although results in mice show no tumorigenicity of human cells, they are not a guaranty for safety.

That poorly characterized stem cells can generate tumours in-vivo in the human has been sadly illustrated by the case of a 13-year old patient in Israel. His parents had taken him three times to Moscow for a stem cell therapy with foetal neural stem cells in a desperate attempt to cure him from ataxia telangiectasia. The result was that the boy developed tumours on his spinal cord. The surgeons who removed the tumours proved that the cells did not belong to the patient, but to at least two genetically different individuals, one of them female (Amariglio et al., 2009; Nature Reports Stem Cells, 2009, www.nature.com/stemcells/).

The final problem, and probably the one most contributing to a false feeling of hope amongst terminally ill patients, is that the literature, and consequently the press, is plagued with reports that seem great at first sight, but in which there are no suitable control groups or have very short-term or exaggerated outcomes.

For instance, in 2008 Geffner and collaborators published that the administration of autologous bone marrow stem cells into spinal cord injury patients improves their quality of life. What the authors do not take into account in their work is that it is known that there is a placebo effect in spinal cord surgery trials that they did not rule out, and that during the surgery they carried out other interventions next to the stem cell infusion for which they did not control in the study (Nature Reports Stem Cells, 2009).

The case of the paper of Bible and collaborators of 2009 is an example of a work with an exaggerated press release. The press release said they could fill a hole left by stroke damage with new brain tissue within seven days. The paper in fact only proved that they could, in rats, fill the hole with a scaffold consisting of little spheres coated with stem cells. The vast majority of the hole was filled with scaffold, and the obtained tissue was unstructured and thin. In addition, it was only a seven-day experiment and further cell survival was not assessed (Nature Reports Stem Cells, www.nature.com/stemcells/).

The fact is that there are at the moment very few stem cell therapies with sufficient medical evidence of success to consider them as yet as acceptable. The best defined and most extensively used one is bone marrow transplantation to treat conditions of the blood or the immune system.

On the other hand, many potential stem cell treatments are currently being tested in animal models and some have already been brought to clinical trials. During the past meeting of International Society for Stem Cell Research in Yokohama (www.isscr.org), several researchers and companies presented their ongoing or recently completed phase I and phase II clinical trials for stem cell therapy. The point all these trials had in common was that the main end point of the study was safety, which is a key issue that all these 'wonder stem cell clinics' unashamedly ignore.

For instance, Ann Tsukamoto of Stem Cells Inc (www.stemcellsinc.com) presented their work using human neural stem cells. These cells are now being clinically assayed to treat two types of neurodegenerative disorders and spinal cord injury. The company also works on the development of a treatment for retinal disorders such as age-related macular degeneration and Alzheimer's disease. The results from their first trials are encouraging, as no tumour formation or problems related to the transplants were observed.

Katarina Le Blanc from the Karolinska Institutet in Sweden spoke about their results on the use of mesenchymal stem cells for the treatment of graft-versus-host disease (Ringden and Le Blanc, 2011). Mesenchymal stem cells seem to have an anti-inflammatory effect, and phase I and phase II studies have shown that 50% of the patients respond to treatment with these cells. These studies were, again, mostly directed to address safety issues. In all the treated individuals, no toxic or inflammatory reactions were found on the short term. In a long-term study, the autopsy of 18 of these patients showed that there was no ectopic tissue formation or tumours, although they could find traces of the DNA from the donor in various tissues of the acceptor (von Bahr et al., 2012).

All in all, the initial euphoria raised by the advent of embryonic stem cells is calming down. In a sense, we tried to run before learning to walk. Now, scientists and clinicians are cautiously looking into realistic clinical applications of stem cells, with the perpetual optimism characteristic of people that spend their lives thinking that the experiment they are doing right now is the last one they need to prove their Nobel Prize worth discovery. And sometimes, they are right.

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