

# An Update on Stem Cell Research

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## Stem cells as replacement cells

Stem cells are immature cells in the body that have not yet developed to the stage when they show a recognizable mature identity, that is, one that would label them as nerve cells, heart cells, liver cells, and so on. These 'uncommitted' cells have some remarkable properties. Firstly, in laboratory conditions they can divide and keep on dividing to produce 'daughter' cells more or less indefinitely, as though they were immortal. Secondly, they are multipotent, or pluripotent, meaning that in appropriate chemical environments they (and their daughters) can transform into any one of a number of distinct adult cell types.

The most attractive feature of stem cells for the medical scientist is the possibility of their being used to replace cells that have died because of disease or trauma. The body actually uses pre-existing stem cells as a repair strategy, providing the particular chemical environment required to get them to develop into the adult cells needed to replenish a depleted population. There are problems, however, in achieving this end experimentally, but before discussing them, let's get this clear at the outset; from the perspective of the Alzheimer community, the interest in stem cell research focuses on one issue – can they be used to replace lost brain cells?

At one time stem cells could be obtained only from embryos or fetuses, in which they are abundant. Human embryos are generally viewed as less than eight weeks old, and fetuses as more than eight weeks old, but before birth. Once in the hands of researchers (actually in the form of cell 'suspensions' made by various techniques designed to break down embryonic tissues so as to get individual cells floating about separately), various chemical treatments are instituted. These use 'trophic' molecules, often compounds identical to those made by the body to support the health of its cells. These molecules also help guide the development of stem cells along the road to becoming specific mature cells, a function that laboratory researchers copy for the stem cells they have 'in vitro', that is in a dish rather than a body (in vivo).

## The new stem cell findings and the media response

Two new research reports, released the week of November 19<sup>th</sup>, 2007, have caused great interest in the scientific community, and great excitement in the media.

What exactly *was* reported, and what was new?

Well, the reports, initially in the form of news releases, emanated from two teams, one in Japan and one in the US. They used a 'retrovirus' as an infecting agent to carry certain molecules known as 'transcription' factors into human skin cells. The Japanese team used skin from the face of a 35-year-old woman, and the US team used foreskin cells from a newborn baby. Transcription factors regulate (activate) other genes. Using the virus, the researchers effectively shuttled up to four

transcription factors into adult human skin cells. These factors were already known to be highly active in stem cells but not in adult cells. The effect of these transcription factors was to activate genes that converted the adult skin cells back into cells that closely resembled normal embryo-derived stem cells. In the jargon, the skin cells were 'reprogrammed'; they lost their original adult skin-like character and instead looked and behaved like normal immature stem cells. Actually, the Japanese workers had earlier shown that this approach worked for rodent skin cells, and the new report essentially extended these findings to human cells. The excitement generated by these two reports was not just because of the discovery of how to transform normal adult cells into stem cells, but because of the implication that *stem cells could now be obtained without the involvement of human fetuses*; this resonated especially with US researchers, who are currently forbidden by law to use human fetal material, even if it derives from fetuses available as consequences of accidental or medically sanctioned abortions. A flood of media speculation was now triggered; stem cell availability, unhampered by ethical or legal constraints, would now soar, promoting undreamed of medical advances, including the replacement of brain cells killed by the Alzheimer's disease process.

### Lost in the excitement

As frequently occurs in such 'breakthrough' situations, earlier scientific findings of great relevance can be lost sight of, almost as if their mention might reduce the drama of the new results. Unfortunately the competitive nature of scientific research can actually promote such forgetfulness, which hopefully does not represent a deliberate state of mind. Over the last six to seven years, Canadian scientists showed that both adult rodent skin and human skin (adult scalp and neonatal foreskin) also harbors *genuine stem cell-like cells*, which with appropriate treatment could be made to develop, for example, into adult nerve cells. For scientists these earlier findings are now of special importance, because of the need to demonstrate experimentally that such already resident stem cells are not confused with or 'contaminating' the manufactured stem cell population described in the new reports.

However, the earlier findings also included a very important result which will be referred to again in the following section, which discusses some of the problems associated with stem cells as replacement cells, for example in Alzheimer brains. The result in question was that although the stem cell-like cells already resident in skin could indeed be transformed into nerve cells, these lacked some critically important electrical properties of normal nerve cells, a defect that would have to be remedied before they could be used as replacement cells in the brain for example.

### Pluses and minuses of stem cells as potential replacement cells

When any foreign tissue or cells are transplanted into a person, their immune system immediately starts to work to get rid of what it views as potentially harmful invaders. This is called 'rejection', and to prevent it the host recipient has to be given immune-suppressants. This is hazardous, because now the body is being deprived of its most important defense against dangerous threats such as infection and the development of tumors. A wonderful advantage of using skin as a source of stem cells is the possibility of using the skin of the patient himself or herself, thereby allowing for a replacement cell strategy without the complication of rejection. This reasoning is a powerful plus in favor of creating a skin-derived stem cell industry.

Moreover, because of the 'immortality' of stem cells already referred to, once they are obtained in a laboratory setting they constitute a persisting source of continuously dividing stem cells that needs no renewal.

Are there drawbacks?

Indeed yes – there always have been problems associated with the idea of a stem cell therapy. These problems apply to stem cells produced from adult skin cells as described in the new reports, just as they did to the earlier-studied embryonic stem cells obtained from fetal tissues, maybe even more so.

Firstly, there is no guarantee that laboratory studied stem cells will eventually convert into totally normal adult cells. As shown in the earlier Canadian studies already mentioned, the adult nerve cells derived from the embryonic-like stem cells discovered in adult skin lacked some critically important mechanisms involved in the signaling role of normal adult nerve cells. There are other concerns as well. The genetic make-up of the stem cells created using retroviral infection of adult skin cells described in the new reports was not identical to that of conventional embryonic stem cells (the activity of about 1000 genes was quite different between the two types of stem cells), and appropriate cautions were mentioned by the authors in this regard.

It's not yet known how abnormal the consequences of these genetic differences are. One major concern is that the use of a retrovirus might introduce the potential for initiating tumors in the host body, or of causing undesirable genetic mutations in neighboring cells. Both of these cautions are mentioned by the authors of the new studies. Moreover, reprogrammed adult skin cells might still contain DNA abnormalities caused by earlier exposure to sunlight or environmental toxins, hazards that could carry over to the newly created stem cell population.

## Conclusions

When all of the above concerns have been satisfied, which will be difficult but not impossible, we still have to address a major issue that comes readily to the minds of neuroscientists, but perhaps less so to molecular biologists and geneticists.

To promote useful functions the implanted neural cells or tissues have to become correctly integrated into the existing neuronal circuitry. The implanted material has to be positioned at the right anatomical sites, the new nerve cells have to be recognized by other nerve cells as appropriate targets with which to make new connections, and they themselves have to grow out nerve fibres that will make connections with the correct receiving nerve cells. Daunting though these problems may seem, there is an unexpected kind of evidence which is supportive of the possibility of implanted nerve cells becoming appropriately integrated into the host nervous system, and even of still immature stem cells developing into adult nerve cells and then undergoing a similar integration.

The results of a variety of studies suggest that cues exist, even in adult nervous systems, which help guide newly-growing nerve fibres to correct destinations. It seems that some of the mechanisms that operate during early development to ensure that the correct connectivity is achieved survive into adulthood. That such mechanisms were once there is clear. Were they absent, and supposing that trial and error were ultimately responsible for ending up with the correct connectivity in the brain,

this would take literally hundreds of years to achieve rather than the months of fetal brain development. So, provided that neuroscientists are able to implant stem cells, or stem cells already transformed into adult nerve cells, into the required brain locations, it could be that enough new connectivity would spontaneously develop to maintain or restore functions threatened by disease or trauma. In the case of Alzheimer's disease, the brain regions involved in memory and cognitive functions would be the prime target of such implantations.

How long will all this take? The best guess of this commentator is decades at the very least. Happily a number of therapeutic approaches that will combat Alzheimer's disease are well advanced in clinical trials, and certainly will be available for general use within some five to seven years, long before stem cell therapy becomes a reality. This is not to deny the potential of such therapy, which offers a direct solution to the loss of nerve cells in the brain. But while we await this desirable result, it's encouraging to know that promising treatments are on the visible horizon.