Significant Developments in Stem Cell Research

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1. Introduction

The object of this Briefing Paper is to provide independent and informed analysis on stem cell research in order to better inform policy makers, members of the legal and medical professions and other interested parties who wish to keep abreast of the latest developments in this field. All information contained within this document has been obtained from sources freely available within the public domain.

2. Definition, Source and Application of Stem Cells

2.1 What are stem cells?

The UK Chief Medical Officer's Expert Advisory Group on Therapeutic Cloning (otherwise known as the Donaldson Committee) defined stem cells in their report entitled ***Stem Cell Research: Medical Progress with Responsibility*** as: *"unspecialised cells which have not yet differentiated into any specific type of tissue."* [1] This definition is consistent with the one applied by the National Institutes of Health, the body appointed, at the time, by President Clinton to consider the value of research using Human Pluripotent Stem Cells (HPSCs).

However, the limitations of this definition were made clear by David A. Prentice, Professor of Medical and Molecular Genetics at Indiana State University, in his testimony before the American Congress in February 2000. Dr Prentice defined stem cells as: *"...cells that can proliferate with almost unlimited potential, maintaining a pool of growing and dividing cells, with the added ability that some of the daughter cells can differentiate into specific cell types."* [2]

This definition accords greater significance to the unique capacity of stem cells to constantly renew themselves, whilst maintaining an ability to adapt to the specific cell types needed by the human body. It is these unique properties that distinguish stem cells from other cell-types in terms of clinical application and that are central to the debate over the use of embryonic versus adult stem cells.

2.2 Sources of stem cells

The human body is a stem cell "gold mine", providing an almost unlimited source of stem cells. However, the problem lies not in locating these cells, but in isolating them from their source. With this in mind, scientists have isolated several key "ready-made" sources of stem cells, often referred to as "reservoirs". The following sources fall within this category:

- Blastocysts - embryos after six days of growth
- Early embryos created by human cloning
- Fetal tissue
- Adult or child tissue
- Adult or child cells that can be grown into stem cells

To date, only stem cells taken from adults or children (known generically as "adult stem cells") have been used extensively and effectively in the treatment of degenerative diseases.

2.3 Application of stem cells in clinical medicine

There are over 4,000 registered diseases specifically linked to genetic abnormalities, as well as a host of others which are thought to have a genetic component. Yet, although stem cells are unlikely to provide fast-track miracle cures for these conditions - and are even less likely to lead to a cure for all known human disease, as certain commentators have speculated - they are unique in their potential application to a large number of these diseases. As tiny factories that have an ability to "re-stock" themselves when required and develop a wide range of specialisms, stem cells meet the technical specifications for use in gene therapy.

Indeed, in many pioneering research projects, completed since the turn of the Millennium, scientists have demonstrated that stem cells can be used to replenish or rejuvenate damaged cells within the immune system of the human body and that damaged stem cells can miraculously repair themselves and their neighbours.

For example, in what is regarded as the first documented case of successful gene-therapy "surgery", scientists at the Necker Hospital for Sick Children in Paris succeeded in treating two infants diagnosed with Severe Combined Immunodeficiency Disease (SCID), a life-threatening degenerative disease caused by defects on the male (X) chromosome. [3] The team extracted "adult" stem cells from the children's bone marrow, manipulated the cells in the laboratory to replace the damaged gene with a functioning gene, then re-injected the cells back into the bone marrow. The repaired cells then "replenished" the immune system and "re-stocked" it with healthy cells.

Indeed, of the more than 60 treatments already available using human stem cells, only adult stem cells are being used in clinical practice. [4] In direct comparison, developments in the field of embryonic stem cells continue to disappoint with not one single proven clinical application. Despite many years of research in animal embryonic stem cells and nearly eight years in the human-embryonic variety, research in embryonic stem cells has often resulted in failure, with a notably high incidence of tumour formation. Experimentation and clinical application using embryonic stem cells is also plagued by the insurmountable fact that, in the words of the report on Human Stem Cell Research of the 11th of September 2003 from the Committee on Culture, Science and Education of the Parliamentary Assembly of the Council of Europe [5]:

"[T]he large number of egg cell donations required for successful use of the technique must be regarded as unacceptable. Not only does this represent an unreasonable burden for the woman concerned, but must also have worrying effects on the self respect and social image of women, if they are seen in this way as 'suppliers of raw materials'."

As the case for embryonic stem cells weakens and experimental failures mount, predictions of eventual success have quietly changed from "years" to "decades", from enthusiastic optimism to muted disappointment.

3. Criteria for the Successful Use of Stem Cells in Medical Research

The UK Donaldson Committee established a very strict set of criteria governing the application of stem cells in research to develop treatments for degenerative diseases. Attempting to strike a balance between the availability and potential of stem cells (from all sources) against the likelihood of their successful application in such research, the Committee specified that:

"The successful application of stem cell research would depend upon:

- *whether stem cells can be successfully isolated and grown in the laboratory*
- *whether stem cells grown in the laboratory can be influenced to turn into specific cell types*
- *whether stem cells that have formed particular cell types could be used to treat patients whose tissue was diseased or damaged through injury*
- *whether tissue grown in this way would develop normally or whether there might be risks to the patient."*

Based on above criteria, the Committee reached the conclusion that so-called "transitional research" is *"warranted across the whole range of possible sources of stem cells in the first instance, including embryos..."*, but with the proviso that the use of embryos be *"...necessary for the purposes of the research..."*

However, whether indeed this research is "warranted across the whole range" of sources, including human embryos, is called into question by the extensive research on the medical application of adult stem cells that has been published since the submission of the Donaldson Committee's Report In January 2000.

4. Stem Cells: Analysis of the Most Up-to-Date Research

The Recommendations made by the Donaldson Committee can only be judged according to the yardstick of the most recent advances in stem cell research.

4.1 Research contradicting the Donaldson Committee's findings

A comparative analysis of the Donaldson Committee's findings against the most up-to-date research (available in the public domain) on the clinical application of stem cells, reveals a significant number of anomalies. The Committee's Report makes misleading, and in some cases totally incorrect, statements about the limited potential of adult stem cells as an ethical alternative to human embryonic stem cells. [6] At this point, it is important to remember that the remit of the Donaldson Committee included the assessment of "...any alternative approaches that might be pursued to achieve the same benefits." [7]

Consider the assertion made in Section 5 of the Report:

"Theoretically, stem cells derived from early embryos have the greatest potential to develop into most types of tissue.[..] Stem cells can be extracted from some adult tissues but their potential to develop into other kinds of tissue is also likely to be limited." [8]

Again, this statement mirrors a claim made more recently by the Institutes of Health in the United States in its Guidelines for Research Using Human Pluripotent Stem Cells. However, research published in recent editions of the Journal of Neuroscience Research and the American Journal Science, revealed that adult stem cells can now be grown into liver or nerve tissue and that human adult stem cells are of "generalised potential". It is therefore a fact that, akin to embryonic stem cells, adult stem cells are now considered by the majority of research scientists to be "pluripotent" (of almost unlimited potential).

Initially published in the April 2000 edition of the Journal Science, the account of this ground-breaking research came three months after the submission of the Donaldson Committee's Report to the Government. And without prior hindsight, the Report concluded that *"(t)his is basic research which if permitted would precede, probably by many years, any possible application to treatment..."*, and further that: *"Most scientists consulted felt that the science was still several years away from being able to deliver many of the technical building blocks needed to make significant progress in achieving healthcare benefits."*

This statement was already out-of-date on the day of the Report's publication. The above evidence makes it clear that adult stem cells are already being used extensively to save or enhance the lives of a significant number of people, whereas embryonic stem cells have yet to really "scratch the surface" in terms of clinical application.

4.2 Significant "healthcare benefits" unique to adult stem cells

Over the past year, adult stem cells have been used either exclusively or in combination with other treatments to achieve significant "healthcare benefits" for sufferers of the following conditions:

- Brain tumours
- Ovarian cancer
- Solid tumours
- Multiple myeloma
- Breast cancer
- Non-Hodgkin's lymphoma
- Multiple sclerosis
- Systemic lupus
- Rheumatoid arthritis
- Anaemia
- Stroke
- Blindness
- Immunodeficiency

Furthermore, the future application of adult stem cells to treatment therapies, where clinical trials have already indicated significant potential benefit, include:

- Parkinson's disease
- Alzheimer's disease
- Nerve damage
- Organ transplantation and/or growth
- Blood production
- Muscle regeneration
- Diabetes mellitus Type I & other pancreatic disorders
- Heart valve replacement

Following on from the specific example given in Section 2.3 [9], documentary evidence of the above cases of successful treatment using adult stem cells can be found in a host of Journals.

Taken in conjunction with the extensive research documenting other successes in the clinical application of adult stem cells, there emerges a clear inconsistency between the position adopted by the Committee and the most recent advances in stem cell research. Adult stem cells, derived from the human body of both adults and children, have clearly "stolen" a considerable "march" on other sources of stem cells in terms of low-risk clinical application.

4.3 Further research confirming the feasibility of adult stem cells

The Report of the National Institutes of Health (NIH), the body charged with advising the United States Government on research using HPSC, also failed systematically to represent the considerable body of research supporting the use of adult stem cells. However, the NIH went a step further than the Donaldson Committee in outlining several very specific reasons why it believed that *"adult stem cells may have more limited potential than embryonic stem cells."* [10]

Firstly, the NIH claimed that *"stem cells in adults are present in only minute quantities"* and are *"...difficult to isolate and purify..."* This contradicts findings published in the March 2000 Edition of the Proceedings of the National Academy of Sciences, which highlighted that adult stem cells can now be grown "billion-fold" in the laboratory. Even the NIH itself recently conceded that stem cells can be produced to provide a "virtually limitless supply". [11]

Secondly, the NIH asserted the opinion that invasive surgery would be required (removal of "a portion of the brain") in order to obtain a source of neural stem cells to treat diseases such as Parkinsons and Alzheimers. However, this is also an outdated claim, given that the June 2000 edition of the journal Nature confirmed that neural stem cells can be regrown inside the brain without the need for open surgery. [12] Research published more recently in the Journal of Neuroscience Research has added further weight to this case confirming that bone marrow cells can now be grown into neural stem cells (brain cells), thereby eliminating the need for invasive surgery. [13]

Thirdly and finally, the NIH claimed that *"stem cells for all cell and tissue types have not yet been found in the adult human."* This statement may have been true when the Report was published but this can also be said of embryonic stem cells (the preferred option according to the NIH). Furthermore, recent editions of Nature Medicine and the British Medical Journal (BMJ) reported that vital adult stem cell types, such as heart and pancreas stem cells, have been identified in animal experimentation, the traditional precursor to clinical use in humans. Further studies have also shown that stem cells can be grown into other types of cells, for example, bone marrow cells into neural cells. Again, the most current evidence contradicts the findings of the NIH.

5. Conclusion

The recommendations made in the Reports of the Donaldson Committee in the UK and the NIH in the US respectively, on the utility of using human embryos as a source of stem cells, and further on the limitations of adult stem cells, are now completely out-dated. Based on the most recent and ground-breaking medical research using stem cells, it has become clear that "adult" stem cells have outstanding advantages in terms of immediate clinical application, safety and feasibility over all other sources of stem cells and that the objections to the use of "adult" stem cells have now been overcome. Objective analysis of the most up-to-date stem cell research has revealed the following key points:

1. Adult stem cells are already being used extensively and successfully in clinical medicine.
2. Stem cells taken from human embryos have significant problems and have limited medical application.
3. Extensive documentary evidence exists to prove that adult stem cells now meet all of the criteria set down by both the Donaldson Committee and the NIH in the U.S.

REFERENCES

1. Stem Cell Research: Medical Progress with Responsibility, Department of Health, Crown Copyright, August 2000.

2. Congressional Testimony of David A. Prentice, Ph.D., http://www.stemcellresearch.org/prentice. htm, February 7, 2000.

3. "Gene Therapy of Severe Combined Immunodeficiency (SCID)-X1 Disease", Science 288, 669-672, April 28 2000.

4. The Coalition of American for Research Ethics, http://www.stemcellresearch.org/facts/treatments.htm

5. Report on Human Stem Cell Research of the 11th of September 2003 from the Committee on Culture, Science and Education of the Parliamentary Assembly of the Council of Europe, Doc. 9902, Paragraph 60.

6. N.B. It is these claims that form the backbone of the case in support of the cloning of human embryos for their stem cells.

7. Stem Cell Research: Medical Progress with Responsibility, Department of Health, Crown Copyright, August 2000.

8. Stem Cell Research: Medical Progress with Responsibility, Department of Health, Crown Copyright, August 2000.

9. The successful treatment of Severe Combined Immunodeficiency Disease (SCID) using adult stem cells.

10. Guidelines for Research Using Human Pluripotent Stem Cells, National Institutes of Health, United States Government, August 2000.

11. Proceedings of the National Academy of Sciences, 97, 3213-3218, 28 March 2000.

12. "Induction of Neurogenesis in the neocortex of mice", Nature 405, 951-955, 22 June 2000.

13. "Adult rat and human bone marrow stromal cells differentiate into neurons", Journal of Neuroscience Research, Issue 61, 364-370, August 2000.