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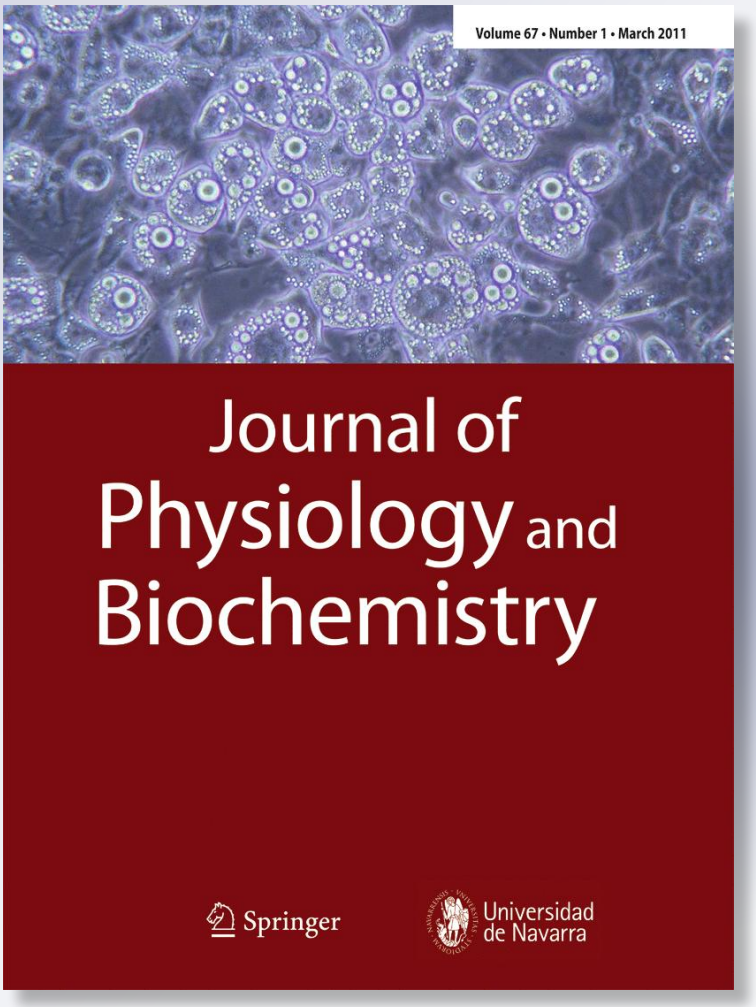

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MINI REVIEW

Embryonic stem cells: are useful in clinic treatments?

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Abstract It is not uncommon to find statements in the social media and even in some scientific journals declaring that embryonic stem cells can be used in human medicine for therapeutic purposes. In our opinion, this statement does not fit the medical reality. To go into this subject in depth, and if possible to clarify it, we reviewed the most recent literature on clinical trials conducted with embryonic stem cells, concluding that up to the present time, there is only one ongoing clinical trial being carried out with these types of cells to treat a small group of patients with spinal cord injury. The results of this trial have still not been published. In conclusion, at present, there is only evidence of one phase I clinical trial conducted with embryonic stem cells, in comparison to the numerous trials conducted with adult stem cells.

Keywords Embryonic stems cells · iPS cells · Adult stems cells · Clinical usefulness

A topic frequently debated in the specialised literature is whether embryonic stem cells have already been used for therapeutic purposes or whether there are at least ongoing clinical trials to this end.

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The stem cells to be used can be obtained from "spare" embryos from in vitro fertilisation or from embryos specifically created for such a purpose by somatic cell nuclear transfer, but deriving stem cell lines from embryos remains a very inefficient process, nearly 4% [20].

In the first case, i.e. if frozen embryos are used to obtain the corresponding stem cells, the therapeutic use of an allogenic material would probably result in the clinical problem of immunological rejection [4]. For this and other reasons, no clinical trials have been performed with derivations of human embryonic stem cells (ESCs) [12].

In the event that cell lines derived from embryos produced by somatic cell nuclear transfer are used, genetic material from the patient himself would have to be used to generate the corresponding zygote. In other words, a human being would have to be cloned. This does not appear to have been achieved up to now.

Nevertheless, despite this, the social media continue to disseminate the therapeutic value of embryonic stem cells, to our mind with the subliminal intent of making their use more easily accepted by society. Given this social reality, we believe it would therefore be interesting to review the current medical literature on the clinical use of embryonic stem cells.

In 2004, DA Prentice [17], in a report of the President's Council on Bioethics, stated that at that time, there were already 57 applications throughout the world (compiled from a peer-reviewed article) which demonstrated improvements in human patients

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using adult stem cells. This list was later increased to about 70 applications [11, 18] and did not include any clinical studies with embryonic stem cells.

As of 20 October 2010, there were 94,093 ongoing clinical trials worldwide [24]. Of these, 3,141 are being conducted with adult stem cells and 11 with embryonic stem cells. However, when we looked closely at this page, we realised that studies 1 and 2 and 9 and 10 have slight differences but they are the same clinical trial. Therefore, there are actually only nine studies that could be included (Table 1). These data appear to confirm the scant, if not non-existent, use of embryonic stem cells for clinical therapeutic trial purposes, but even so, we believe that nine clinical trials is a significant figure. Consequently, we thought it interesting to analyse these nine trials more thoroughly, to check if they were aimed effectively at the therapeutic use of embryonic stem cells.

Of the nine aforementioned trials (Table 1), two of them, numbers 5 [19] and 7[8], were conducted with iPS cells, not with embryonic stem cells. Another five trials, numbers 2 [15], 4 [16], 6[14], 8 [22] and 9[13], had been carried out with stem cells from adult tissues and there were only two, numbers 1 [9] and 3[21], in which embryonic stem cells had been used. However, on analysing these two studies in more depth, it was observed that none of them were clinical trials conducted for therapeutic purposes, but were studies with an experimental end.

In other words, as far as we know, there are no clinical trials for therapeutic purposes conducted with embryonic stem cells at the present time.

Regardless of the above statements, we believe that up to the end of April 2010, there was only one ongoing clinical trial and another one planned using embryonic stem cells. In fact, at the end of 2008, three North American companies had presented proposals to the FDA to conduct clinical trials with embryonic stem cells [6]. The first, Geron, wished to perform clinical experiments with embryonic stem cells for the treatment of spinal cord injuries; Novocel [6] was looking at directing human embryonic stem cells into glucose-responsive insulin-secreting cells aimed at treating diabetes, and finally, Mytogen was focused on developing retinal-pigmented epithelial cells from human embryonic stem cells to treat patients with macular degeneration. The three proposals were rejected by the FDA, pointing out that before conducting clinical trials in humans, it was necessary to complete certain safety tests and to carry out animal experiments, which in their opinion had not been done.

Table 1 Possible clinical trials conducted with embryonic stem cells

Rank	Status	Study	Centre	Type of cells used	Reference
1	Recruiting	The derivation of human embryonic stem cell lines from PGD embryos	Hadassah Medical Organization	Embryonic cells	[9]
2	Recruiting	Studying breast stem cells from patients with cancer and from healthy individuals	National Cancer Institute	Adult cells	[15]
3	Active, not recruiting	The role of TBX3 in human ES cell differentiation	University of California	Embryonic cells	[21]
4	Recruiting	Isolation and characterization of mammary stem cells	National Institutes of Health	Adult cells	[16]
5	Recruiting	Patient-specific induced pluripotency stem cells (PSiPS)	Royan Institute	iPS cells	[19]
6	Recruiting	Evaluation of circulating levels of adult stem cells in the peripheral blood of patients with acute decompensated heart failure and following stabilization, in comparison with healthy volunteers (CIRCSTEM-HF)	Monash University	Adult cells	[14]
7	Active, not recruiting	Development of iPS from donated somatic cells of patients with neurological diseases	Hadassah Medical Organization	iPS cells	[8]
8	Recruiting	The transendocardial autologous cells (hMSC or hBMC) in ischemic heart failure trial (TAC-HFT)	University of Miami	Adult cells	[22]
9	Recruiting	Molecular characterization of neuroblastic tumor: correlation with clinical outcome	Memorial Sloan-Kettering Cancer Center	Adult cells	[13]

Information obtained from www.clinicaltrials.gov (references [8, 13–16, 18, 19, 22, 24])

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Rather surprisingly, however, on 23 January 2009, 3 days after Obama became president of the United States, Geron's project was approved [7]. As mentioned previously, this clinical trial is aimed at treating patients with spinal cord damage with embryonic stem cells. Eight to 10 patients who had suffered a severe spinal cord injury in the previous 2 weeks were to be included [23]. The results of a phase I trial are expected to be known at the end of this year, 2010, or early 2011 [1].

Subsequent to the approval of this first clinical trial, another was proposed [10] in which it was hoped to create a tissue from embryonic stem cells, similar to that destroyed in patients with age-related macular degeneration. The cells created will be placed on an artificial membranous support, which will then be inserted in the macula. It is planned to conduct a small pilot trial with a dozen patients, to be carried out between 2010 and 2012.

Encouraged by these proposals, other companies such as Neuralstem, Biotime, ACT and Stem Cells [1] have also expressed their desire to initiate clinical trials using embryonic stem cells; Neuralstem wishes to evaluate the usefulness of embryonic stem cells in the treatment of amyotrophic lateral sclerosis and Stem Cells in the treatment of Peliazeus–Merzbacher disease, a childhood neurological disorder which generally leads to premature death in these patients [1].

So, why are there hardly any clinical trials with embryonic stem cells? In our opinion, apart from the ethical reasons against these studies (it should not be forgotten that to obtain embryonic stem cells, the embryos which donate them must be destroyed), it may be due to the inefficiency of the cloning process, lack of knowledge about the biological mechanisms which regulate these processes, the need for the patient receiving the graft to remain on immunosuppressant therapy for their entire lives and above all, due to the risk of inducing the development of teratomas [12]. As James Thomson and James Gearhart state [1], "there is a great concern among many of us about the possibility that some patients included in these studies could develop tumours, which would be an authentic disaster". This has already happened. In February 2009, an Israeli child with ataxia telangiectasia who had received several foetal stem cell transplants developed teratomas in the brain and spinal cord 4 years after having commenced treatment [2]. For that reason, M. Enserink stated a couple of years ago [5] "that no-one today could promise the falsehood that anyone can be cured with embryonic stem cells in the near future; this is to cruelly deceive patients and the public".

In other words, we believe it can be stated, without fear of contradiction, that up to now, there is only one clinical trial conducted with embryonic stem cells and a great number carried out with adult stem cells. In this respect, and to avoid referring to the extensive literature on this topic, we consider it of interest to highlight a magnificent review published recently [3], in which it was shown that of 926 clinical trials evaluated, only 323 offered sufficient technical guarantees to be considered valid; of these, the authors who wrote the paper selected 69 as suitable, of which 26 were aimed at the treatment of autoimmune diseases and 43 at vascular diseases.

Undoubtedly, all of the above data support the potential usefulness of adult stem cells, in the more or less near future, in regenerative and reparatory medicine, something which does not appear likely with embryonic stem cells for the time being.

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