

Stem cell therapeutics—reality versus hype and hope

Nicolas H. Zech · Karl-Heinz Preisegger ·
Peter Hollands

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In the last decade medical science has started to make the first steps towards a paradigm shift from repair to regeneration [1]. The potential use of a range of stem cells in regenerative medicine is currently one of the most intensively researched areas worldwide [2]. In particular, embryonic stem cells (ESC) and more recently Induced Pluripotent Stemcells (iPS) [3] have provoked a lot of interest as a potential source of stem cells in the treatment of diseases such as Alzheimer's and Parkinson's diseases.

Capsule Human cord blood stem cells have a realistic and proven potential for the treatment of various diseases compared to embryonic stem cells / iPS cells.

N. H. Zech (✉)
IVF Centers Prof. Zech - Bregenz,
Roemerstrasse 2,
6900 Bregenz, Austria
e-mail: n.zech@ivf.at

N. H. Zech
Unit of Gynecological Endocrinology and Reproductive
Medicine, University of Graz,
Graz, Austria

K.-H. Preisegger
Medical Director Vivocell Biosolutions,
Statteggerstr. 60,
8045 Graz, Austria

P. Hollands
Senior Lecturer in Biomedical Science,
University of Westminster,
115, New Cavendish Street,
London W1W 6UW, UK

Nevertheless, these hopes have not yet been fulfilled with either ESC or iPS.

Murine ESC were first described in 1981 [4] and subsequent studies showed the regenerative potential of murine stem cells derived from both pre- and post-implantation embryos [5–7]. This early murine work was followed by the development of human ESC in 1998 [8]. Both murine and human pre-implantation ESC are derived from the inner cell mass (ICM) of the blastocyst at day 5/6 of growth. The ICM consists of primitive ectoderm cells, which subsequently develop into epiblast cells in post-implantation embryos. Despite these ontogenic similarities human and murine ESC do not resemble each other in many aspects [9]. For example, murine ESC rely on leukemia inhibitory factor (LIF) and bone morphogenic protein-4 (BMP4) for maintenance of pluripotency [10, 11], whilst human ESC are dependent on TGF β /Activin/Nodal pathway activity and fibroblast growth factor-2 (FGF2) [12–17] and thus resemble epiblast stem cells (EpiSC). Usually EpiSC cannot be reverted to a state such that they respond to LIF and BMP4. Furthermore, primordial germ cells, which originate from pluripotent epiblast cells in mice, respond in a similar way to LIF and BMP4, such as murine ESC derived from the ICM [18]. Additionally, murine ESC can be cultured as single cells while human ESC are particularly sensitive to dissociation and should be cultured in clumps [19].

There are clearly many basic concepts still to be explored in the biology of ESC of various species. Thorough understanding of these cells is still in its' infancy despite 20 years of basic research. Bearing this in mind there should be an air of caution when proposing future clinical applications. Can or should we move forward into thinking about clinical applications when the fundamentals

of ESC pluripotency are yet to be fully understood? Currently iPS are provoking much hype and hope for potential therapeutic applications in the future [20]. Despite the fact that murine ESC have been studied for 20 years and human ESCs for 10 years there is still little true understanding of their biological properties. Now iPS are part of the discussion and their role is proposed repeatedly as a source of stem cells for future regenerative medicine procedures. Nevertheless, the basic biological properties of iPS have yet to be understood and before these are known any thoughts about clinical use are both premature and potentially dangerous.

There is a saying “It’s hard to make predictions—especially about the future”. Nevertheless, anyone with any experience at all in medical research and the introduction of new technologies knows how arduous it is to develop new and safe medical therapeutics. Bearing this in mind it is much too early to raise big hopes on the potential therapeutic applications of human ESC and iPS. Such plans may never come to fruition or even if they do there may be severe restrictions on their use in routine clinical practice. The pharmaceutical industry bears witness to this in that new pharmaceuticals can take many decades of development before they are considered safe for general use [21]. Even though there would be an iPS or ESC preparation in the pipeline for therapeutic application, such as with promising drug targets, it would take at least 10–15 years to bring it to the market. It could take years to develop a specific iPS or ESC “therapeutic” for a certain disease, which would have to undergo the specific clinical trials. It is hard to imagine, that there could be many different such “therapeutics” developed for even the most common diseases in a short time frame. Even if pluripotency could be better understood and the risks of teratoma formation [22] overcome, the creation of iPS in a more controlled protocol would be required to even contemplate clinical applications. This would need the removal of viral transfection to establish iPS and silencing of the *Ink4/Arf* locus complex, which is overexpressed in older cells and thus a barrier for successful reprogramming. It is also important to note that the *Ink4/Arf* locus is involved in cancer resistance and inhibition of this locus might expose cells of the elderly to an additional risk for malignant transformation [22–25].

In 2008, Trounson *et al.* [26] published a commentary where it is clearly stated that the road ahead leading to stem cell therapies and possible cures (using human ESC) may be long and arduous. What was the basis behind this statement? It is related to the California Initiative embodied in Proposition 71, which was designed to boost ESC research and its translation into cell therapies. This initiative has thus far failed to realise the big hopes it proposed. This

is a classic example of ‘hype and hope’ where large amounts of money were put into this research and people wanted to see the results. Unfortunately neither the promise nor the results have to date been achieved.

Similar statements, this time concerning cloning, were made by Scolding in 2005 [27]. Current iPS technologies can be regarded as substitute for cloning and, in our opinion, the statements also hold true for such cells. In the same article it is stated that “...safety data from 50 years of clinical bone-marrow transplantation....accompanying clinical expertise in collecting, handling, freeze-storing, thawing, and delivering marrow, have safely allowed a rapid translation of bone-marrow stem-cell science from laboratory to clinic”.

It seems that history is (not surprisingly) repeating itself with regard to hype and hope for rapid translation of ESC and iPS science into possible cures. There are some people who warn on stem cell hype such as Lord Winston, a fertility expert and president of the British Association for the Advancement of Science from 2004 to 2005. There was a headline in BBC news in September 2005 [28] “Winston warns of stem cell ‘hype’”—The potential benefits of embryonic stem cell research have probably been oversold to the public, fertility expert Lord Winston says. He fears a backlash if science fails to deliver on some of the “hype” around the cells—as he believes may happen. Yamanaka, the pioneer of iPS, warned against hype in 2008 [29] stating: “It is quite dangerous to predict (meaning: giving a timetable for the development life-saving treatments that could follow his work on iPS cells). If I say 5 years for some disease, patients suffering from that disease will expect it. After 5 years they may be very disappointed. I think we should avoid too much hype”.

The Geron Corporation in the USA recently started the first human ESC clinical trial in patients with spinal cord injuries using their proprietary ESC product GRNOPC1 [30]. In May 2009, the following headline was posted by Nature news [31]: Gene therapy researcher warns stem-cell scientists not to repeat his field’s mistakes. When James Wilson, a gene therapy researcher, who directed a clinical trial on gene therapy with fatal outcome was asked by Nature news why he is speaking up now, he responded “The morning I saw all the hype around the announcement regarding Geron’s approval to proceed with clinical trials [32], I was very concerned that stem cells might be headed along the same path as gene therapy. I wanted to do what I could to avoid the rise-and-fall phenomenon that we saw in gene therapy with stem-cell research”.

Contrary to ESC and iPS, stem cells from adult tissue and especially those from umbilical cord blood have a realistic and proven potential for the treatment of various

diseases in the autologous and allogeneic transplants, with more than 20,000 transplants for around 80 different blood disorders completed to date [33]. It is clear that umbilical cord derived haemopoietic stem cells are a serious and clinically effective alternative to bone marrow (BM) transplantations [34].

Recently mesenchymal stem cells derived from umbilical cord blood, bone marrow and adipose tissue have been shown to have significant potential in regenerative medicine [35]. Unlike ESC, large amounts of adult tissue derived mesenchymal stem cells can easily be recovered at low costs and without the need for additional culture expansion. These mesenchymal stem cells appear to be a much more available and cost effective long term solution in the search for stem cells to use in clinical practice.

There are more than 10,000 patients searching daily for a suitable allogeneic bone marrow stem cell donor in the Bone Marrow Registries. Often these patients have to suffer and may die, because no suitable donor can be found. Such patients could benefit from an umbilical cord blood stem cell transplant if such cells were readily available to everyone. Additionally, many thousand patients per year (in Europe alone) undergo transplants using their own old and/ or diseased stem cells for therapy [36]. These patients may also benefit from an umbilical cord blood stem cell transplant if cord blood was banked in sufficient amounts. However, cord blood banks need the financial resources and must meet the international quality standards to safely collect, store and release such cells for transplant. In 2004 The New York times reported “*there may be only 20,000 to 25,000 usable units available.... in the absence of federal coordination, the industry seems unable to organize itself... in a kind of Catch-22, the lack of a fully functioning system has curbed demand by transplant doctors for umbilical cord blood, leaving the blood banks without the money to collect and store significantly more units*” [37]. Since then, not much seems to have changed. Scaradavou *et al.*, (2010) states that “*...20% of (UCB) units had low CD34+ cell viability, with viability varying according to the bank of origin*”, which leads to a low probability of engraftment [38].

We all have to acknowledge that the public domain is often poorly funded and lacks the organizational spirit of private companies. When collecting umbilical cord blood for the public benefit, we should take this into consideration and allocate public funding accordingly. Stem cell technology is clearly in its’ infancy and we must keep all scientific options open if there are to be stem cell treatments in the future. We believe that umbilical cord blood and the stem cells it contains represent a critical component of future stem cell treatments. A concerted and concentrated effort is needed by everyone involved

to ensure that we maximise cord blood collection and storage. This will minimise hype and maximise hope!

Conflict of interest Karl-Heinz Preisegger is Medical Director of Vivocell Biosolutions

Nicolas H. Zech is board member of Vivocell Biosolutions

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