Bench-to-bedside translation of stem cell therapies: where are we now and where are we going?

“...it is important to know that there are no stem cells that provide a cure for everything and everyone.”

First draft submitted: 19 April 2016; **Accepted for publication:** 20 April 2016; **Published online:** 18 May 2016

Keywords: bystander effect • cell replacement • stem cells • transplantation

We are currently confronted with daily adverts touting miraculous cures based on stem cells form virtually any disease. This situation increases the distress of patients who, while having an urgent need to know the real hope for success of truly effective therapies, perceive lack of appropriate information channels, which would help them make conscious and informed decisions.

In order to understand stem cell mechanisms of action, it is important to know that there are no stem cells that provide a cure for everything and everyone. Therefore, generalization could be misleading. In some cases, stem cell treatments already exist and are routinely used in therapy. From 1957 up to now, in the world, more than 1 million of hematopoietic stem cell transplants (i.e., bone marrow transplantation) have been carried out to treat patients affected by more than 70 malignant and nonmalignant forms of blood disorders [1]. Over the past 20 years, the skin stem cells have treated not only thousands of patients with serious burns but they have also healed hundreds of people with vision problems caused by damage to the cornea [2]. In these two areas, the data are real and reliable, but the evidence of real healing power of stem cells in other contexts is not clear owing to the experimental available results that are neither solid nor unambiguously interpreted. Thus, further testing and confirmation are required. Nevertheless, as paradoxical as it may seem, these latter situations, when used by the media, induce miraculous expecta-

tions. Besides, it can be often heard about an alleged ideological barrier, introduced by the international scientific community, regarding the use of stem cells. Having in mind that a treatment should not jeopardize a patient's life, it is reasonably understandable that every treatment must be proved safe, before it is put into use and declared effective.

This cautious approach by the world wide scientific community is imperative owing to the fact that there are many questions to be answered before foresee a large-scale use of these new therapies. Just to list few of them:

- What are stem cells used for?
- Where to pick them up?
- Which ones should be used: embryonic, adult or fetal?
- Where should they be collected: from the heart, blood or fat?
- Which is the best route for cell administration?
- Which are the side/toxic effect stem cells may cause once *in vivo* transplanted?

Considering the data collected so far, in order to treat people in need of care, it is not enough to identify a stem cell type and grow it in a laboratory. The therapeutic approach must be disease specific, as it cannot be talked about stem cells in a generic way, without dwelling on the fact that there are profound

Gianvito Martino

Neuroimmunology Unit, Institute of Experimental Neurology, Division of Neuroscience, San Raffaele Scientific Institute & Vita Salute San Raffaele University, Via Olgettina 58, 20132 Milan, Italy
Tel.: +39 0226434958
Fax: +39 0226434855
martino.gianvito@hsr.it

differences between the different stem cells, as well as between the various diseases. If stem cells are used to treat blood cancers, it should not be concluded that the same cells would be equally effective in treating brain tumors. It should be simply admitted that even today there is little understanding of the basic mechanisms that regulate the functioning of these cells.

First of all, stem cell-based therapies are more heterogeneous than we thought only a few years ago, thus different strategies can be envisaged depending on the type of disease that such therapies need to confront with. In focal diseases in which cellular degeneration is the primary event and the area of damage is very well demarcated, cell replacement is the most desirable effect. In this situation, committed precursors with limited differentiating options and high integrating ability can be nowadays considered the most appropriate cellular sources to be transplanted intraparenchymally within the damaged area [3,4]. On the other hand, in multifocal diseases where the damage has spread throughout the affected tissue multisite surgery is too risky and complicated, thus safer routes for cell delivery should be explored. Recent evidence suggests that the cells could be introduced through the blood and/or the cerebrospinal fluid but those data should be considered still experimental [3–5].

“Although there is still a long way to go, stem cells can be nowadays considered a potentially useful and effective therapeutic tool.”

Moreover, there is a level of uncertainty connected to the simple transplantation of the cells, as the *in vivo* mechanisms of action of stem cells are not completely clear. There is an opinion, quite perfunctory, that stem cells rebuild tissues by replacing damaged cells. Recent studies have provided data showing that stem cells might also prevent damage and rebuilt tissues by producing *in situ* a milieu of tissue protective molecules – for example, immunomodulatory substances, trophic growth factors, stem cell regulators, angiogenic factors, scavengers, among others – whose release is regulated, both temporally and spatially, by environmental demands, the so called ‘bystander effect’ [3]. All these tissue protective molecules are constitutively expressed by somatic stem cells for maintaining tissue homeostasis during development and adulthood as recently demonstrated for neural stem/precursor cells (NPCs) [6,7], which are also the very first stem cell type shown to be capable of adopting the bystander strategy to protect the central nervous system from inflammatory and degenerative insults once *in vivo* transplanted [3–5,8–11]. Subsequently, similar bystander functions by other types of somatic stem cells (e.g., mesenchymal stromal cells) have been described [12]. All those data together strongly suggest the ability of transplanted stem cells to protect

tissues from diverse injury using multifaceted strategies, from cell replacement to bystander effect. The concept of ‘therapeutic plasticity’ is therefore now emerging and also reconciles data showing that stem cells may have a beneficial role in tissue repair although endowed with negligible transdifferentiation capability [3,4,12].

As a consequence of this plasticity, more efficacious therapies may result from the possibility of exogenously regulating the different therapeutic effects stem cells may exert *in vivo* upon transplantation. To reach this goal, however, we first need to understand the best way to tightly control and regulate the various stem cell-mediated therapeutic functions that might, in certain conditions, become detrimental. Due to the bystander effect exerted *in vivo*, stem cell transplantation is not without risks and in particular when stem cells are transplanted heterotopically and not orthotopically. Cotransplantation of NPCs and pancreatic islet cells under the kidney capsule of diabetic mice induced the generation, at the site of cell transplantation, of insulin-induced neuroblastoma-like neoplasms [13]. Intracardiac transplantation of stem cell factor overexpressing MSC into mice with myocardial infarction promoted the formation of a chest wall-invading soft tissue sarcoma [14]. The unregulated transplantation of autologous hematopoietic CD34⁺ stem cells into the renal parenchyma of a patient with lupus nephritis resulted into an angiomyeloproliferative lesion [15]. In a similar setting, intracerebellar and intrathecal injection of poorly characterized fetal-derived nervous tissue into a boy with ataxia telangiectasia evolved into a heterogeneous proliferative mass [16]. Last but not least, 9 months after an initial diagnosis of multiple sclerosis, a 17-year-old girl underwent stem cell transplantation in Costa Rica; a therapeutic attempt that caused a sudden deterioration of the patient which was transported back to the USA with headache and vomiting progressing to quadriplegia, locked-in syndrome and superimposed encephalopathy [17].

Although there is still a long way to go, stem cells can be nowadays considered a potentially useful and effective therapeutic tool. However, admitting that the procedure is full of unknown possible outcomes, it must be done within a strict and checkable protocol, where common rules may not be waived. For this reason, several Phase I/II trials in humans – testing the safety and the efficacy of several types of stem cells in several disorders – are ongoing in these days and preliminary results will be available in the next few years [18]. Nevertheless, the flourishing world of so-called specialized centers for therapies based on stem cells, which do not undergo strict quality control and often make their own profit the only reason for existing, certainly does not facilitate the demanding task of proving, without any doubt, that stem cells might

represent a realistic therapeutic option [19]. Thus, it is important that these considerations are taken into account by the entire community and new legislative tools should be developed to protect the patients, made vulnerable by need of care and hope. It is these issues that make the boundary between science and consciousness transient and it is here that citizens need and have the right to be protected and instructed to make an informed choice.

Investment in this sector of research should be increased, mainly using public funds to avoid drifts linked to profit. Evidently this is a lengthy process that takes time. This does not mean that it will take several decades before the large scale application of therapies based on the use of stem cells becomes widely applied. Nevertheless, it means that it should not be expected that currently existing complex problems could be solved overnight. In summary, until the basic mechanisms that regulate stem cell function are determined, all triumph is misplaced.

References

- 1 Thomas ED, Lochte HL Jr, Lu WC, Ferrebee JW. Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. *N. Engl. J. Med.* 257, 491–496 (1957).
- 2 Rama P, Matuska S, Paganoni G, Spinelli A, De Luca M, Pellegrini G. Limbal stem-cell therapy and long-term corneal regeneration. *N. Engl. J. Med.* 363, 147–155 (2010).
- 3 Martino G, Pluchino S. The therapeutic potential of neural stem cells. *Nat. Rev. Neurosci.* 7, 395–406 (2006).
- 4 Kokaia Z, Martino G, Schwartz M, Lindvall O. Cross-talk between neural stem cells and immune cells: the key to better brain repair? *Nat. Neurosci.* 15, 1078–1087 (2012).
- 5 Pluchino S, Quattrini A, Brambilla E *et al.* Injection of adult neurospheres induces recovery in a chronic model of multiple sclerosis. *Nature* 422, 688–694 (2003).
- 6 Butti E, Bacigaluppi M, Rossi S *et al.* Subventricular zone neural progenitors protect striatal neurons from glutamatergic excitotoxicity. *Brain* 135, 3320–3335 (2012).
- 7 Martino G, Butti E, Bacigaluppi M. Neurogenesis or non-neurogenesis: this is the question. *J. Clin. Invest.* 124, 970–973 (2014).
- 8 Pluchino S, Zanotti L, Rossi B *et al.* Neurosphere-derived multipotent precursors promote neuroprotection by an immunomodulatory mechanism. *Nature* 436, 266–271 (2005).
- 9 Bacigaluppi M, Pluchino S, Kilic E *et al.* Delayed post-ischemic neuroprotection following systemic neural stem cell transplantation involves multiple mechanisms. *Brain* 132, 2239–2251 (2009).
- 10 Cusimano M, Brambilla E, Biziato D *et al.* Transplanted NPCs instruct phagocytes to remodel the injured spinal cord tissue. *Brain* 135, 447–460 (2012).
- 11 Laterza C, Merlini A, De Feo D *et al.* iPSC-derived neural precursors exert a neuroprotective role in immune-mediated demyelination via the secretion of LIF. *Nat. Commun.* 4, 2597 (2013).
- 12 Ottoboni L, Defeo D, Merlini A, Martino G. Commonalities in immune modulation between mesenchymal stem cells (MSCs) and neural stem/precursor cells (NPCs). *Immunol. Lett.* 168, 228–239 (2015).
- 13 Melzi R, Antonioli B, Mercalli A *et al.* Co-graft of allogeneic immune regulatory neural stem cells (NPC) and pancreatic islets mediates tolerance, while inducing NPC-derived tumors in mice. *PLoS ONE* 5, e10357 (2010).
- 14 Fazel SS, Angoulvant D, Butany J, Weisel RD, Li RK. Mesenchymal stem cells engineered to overexpress stem cell factor improve cardiac function but have malignant potential. *J. Thorac. Cardiovasc. Surg.* 136, 1388–1389 (2008).
- 15 Thirabhanjasak D, Tantiwongse K, Thorner PS. Angiomyeloproliferative lesions following autologous stem cell therapy. *J. Am. Soc. Nephrol.* 21, 1218–1222 (2010).
- 16 Amariglio N, Hirshberg A, Scheithauer BW *et al.* Donor-derived brain tumor following neural stem cell transplantation in an ataxia telangiectasia patient. *PLoS Med.* 6, e1000029 (2009).
- 17 Alderazi YJ, Coons SW, Chapman K. Catastrophic demyelinating encephalomyelitis after intrathecal and intravenous stem cell transplantation in a patient with multiple sclerosis. *J. Child. Neurol.* 27, 632–635 (2012).
- 18 Li MD, Atkins H, Bubela T. The global landscape of stem cell clinical trials. *Regen. Med.* 9, 27–39 (2014).
- 19 Baker M. Stem cell therapy or snake oil? *Nat. Biotech.* 23, 1467–1469 (2005).

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.