The "great expectations"[1,2] of regenerative medicine

Regenerative medicine is currently considered one of the fields of major interest for the progress of medicine. In fact, there is a diffuse expectation that regenerative medicine holds a strong potential to deliver new treatments for serious diseases and injuries for which today few effective treatments exist. The US National Institute of Health defined regenerative medicine as "the process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage, or congenital defects". Research about regenerative medicine encompasses embryonic, fetal and adult tissue stem cells. Any stem cell can self-renew (generate perfect copies of themselves upon division) and differentiate (produce specialized cell types that perform specific functions in the body). The promise of stem cells as new tools for benefiting human health resides in these twin properties that, in principle, allow production of unlimited quantities of defined cell types (e.g., for use in drug screening or transplantation). Furthermore, stem cells enable the human tissues to grow, repair and renew themselves. Beyond this primary definition, stem cells are classified into two major sub-types, based on the range of specialized cells they can generate: tissue (or adult) stem cells, and pluripotent stem cells.

Tissue (or adult) stem cells are found throughout the body, where they function to maintain the organ or tissue in which they reside, throughout the lifespan. Under normal physiological conditions, each type of tissue stem cell only generates cells of the organ or tissue system to which it belongs: the blood (hematopoietic) stem cell generates blood, the skin stem cell generates skin, and so on. Pluripotent stem cells, in contrast, have the potential to generate any type of cell found in the body. Pluripotent stem cells are generated in the laboratory by capturing or recreating cell types that exist only transiently during embryonic development, and have not been identified in the adult body.

There are currently three types of pluripotent stem cells, each generated by a different route: embryonic stem cells, epiblast stem cells, and induced pluripotent stem cells.

Embryonic stem (ES) cells are derived from early-stage, pre-implantation embryos, and were the first type of pluripotent stem cells to be discovered: first in mice and then in humans and several additional species.

Epiblast stem cells are a type of pluripotent mouse stem cells derived from a slightly later stage of embryonic development than mouse ES cells; they more closely resemble the hES (human embryonic stem) cells.

Induced pluripotent stem (iPS) cells were discovered in 2006 using mouse cells by Shinya Yamanaka; just a year later, this finding was replicated in human cells. iPS cells are generated from specialized cells by using a technique called "reprogramming". This groundbreaking work was awarded the Nobel Prize in Physiology or Medicine in 2012. Researchers have rapidly adopted iPS cells for study, although there is on-going discussion in the field about whether they are completely interchangeable with ES cells.

A recent report by EuroStemCell, Kyoto University, and Elsevier showed that stem cell research is growing more than twice as fast as the world average growth in research. Moreover, stem cell publications are now twice more cited than the world average for all related subject areas, with induced pluripotent stem cells (iPS) associated with higher citation rates. Countries with the highest relative activity levels in stem cell research were: Singapore (1.8 times the global level), Italy (1.65 times the global level), the USA (1.61 times the global level), Japan (1.53 times the global level), and Israel (1.52 times the global level). The greatest increase in relative activity in stem cell research between 2008 and 2012 was observed in Singapore and Korea. In Singapore, this likely reflects significant investment in the field. Korea's government has also made stem cell research a strategic life science research focus. It's quite surprising for me as Italian to find Italy among the top Countries where stem cells research is more active because is well known that Italy is among the European Countries with the lowest gross domestic expenditure on research and development (source EuroStat at: http://epp.eurostat.ec.europa.eu/portal/page/portal/science_technology_innovation/). Furthermore, Italy has one of the world's most restrictive legislation about embryonal stem cells research. So, Italian investigators doesn't matter if they can't research on embryonal stem cells anyway. Actually, EuroStemCell reported a notable decrease of activity in human embryonic stem cell research and increased activity in induced pluripotent stem cells all around the world, but the high scientific activity of Italy in this field of research deserves particular attention for another reason. A highly emotional debate on Italian media and public opinion there is about a new therapy based on an unproven and unpublished stem cells therapy for neurodegenerative diseases, called Stamina. Quite surprisingly, the Stamina Foundation insists that its therapy can only be prepared by its own people, without using good manufacturing practice (GMP). The International

[1] Great Expectations - The Gaslight Anthem, The '59 Sound, SideOneDummy 2008.

[2] Great Expectations by Charles Dickens, London, Chapman & Hall Eds, 1861.

Society for Stem Cell research (ISSRC) intervened with a communication made by Shynia Yamanaka who spoke strongly against any stem cell-based treatment proposed outside patient protection rules.
No details of the Stamina therapy or clinical protocols were provided by the owners of Stamina, referring instead to the scanty methods in his 2010 US patent application. That describes a method for promoting the differentiation of bone-marrow- derived stem cells into other cell types for therapeutic use, and includes two micrographs purporting to document the successful creation of nerve cells. Both, Nature revealed, were lifted from papers published by Ukrainian and Russian scientists (see Nature http://doi.org/ m57; 2013). The previous Italian Government sponsored a €3-million (US$3.9-million) clinical trial of the technique pushed by public demonstrations organized by families of patients who see it as their last hope. Now, recognized Italian scientists – as well as some politicians – are questioning whether the Italian ministry of health should continue with the Stamina trial, but some public prosecutors forced to go on with the Stamina's compassionate trial because of humanitarian reasons. Although there are no scientific reasons to justify the trial, Italian officials have mooted a legal one. Various courts in Italy have ruled that individual patients demanding compassionate therapy from Stamina have the right to it, whereas others have ruled that they do not. While it is now unlikely that a formal clinical trial will ever take place, it remains unclear whether patients will continue to receive the treatment.
However, a human experimentation to settle pure legal differences of opinion is not ethically justified. To date there's no evidence about the Stamina method reported by peer-reviewed sources. Individual experiences, anecdotal sources and video witnesses are not scientific proofs.
Considerable research effort addresses the fundamental biology of stem cells in normal and diseased states, and is required to both advance the field and improve understanding of wider biological principles. Today, a great effort is still required to understand how stem cells can repair and regenerate ill tissues before to treat illness.
As Akihiro Umezawa, director of the Department of Reproductive Biology and Pathology at the University of Keio in Japan, says: "Society has high expectations toward stem cell research. I hope society will be tolerant enough to support and nurture an atmosphere where challenge is welcomed. Not all research always sees its light and there are countless errors behind the scenes. Science builds upon the footprints of other researchers, and encouraging challenge is what strengthens the research power of a nation as a whole...In translational research, scientists are there to provide evidence to inform risks. It's then for society to judge whether that should be brought to the clinic".

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