Science and Ethics: Bridge to the Future for Regenerative Medicine

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The objective of this article is to reflect on the relationship between regenerative medicine and ethics, using as references the Aristotelian concept of what is ethical and that of Raessler Van Potter about bioethics. To do this, I will briefly describe the advances in regenerative medicine with stem cells, the strategies for producing pluripotent cells without destroying human embryos, and the great potential of stem cells to improve life for Humanity, noting that for this to be possible, it is necessary to locate the role of regenerative medicine in the context of human values and well being. In this way, this article has a real perspective of the role that regenerative medicine can play in benefitting human beings and engendering respect for human and natural environments.

Keywords: Stem cells, Regenerative medicine, Bioethics, Science and human values

Introduction

Science and Ethics, Bridge to the future, brings to mind the visionary intuition and reflection of Van Rensselaer Potter in his famous book in which he introduced the concept of bioethics, which implies essentially and urgently the re-encounter of biology and philosophy, in the strict sense of “love of wisdom” (1).

I will begin by pointing out that ethics in its foundation is a discipline that helps us in living a good life. In his *Nicomachean Ethics*, Aristotle points out that we all seek what is good: “Let us resume our inquiry and state, in view of the fact that all knowledge and every pursuit aims at some good. Verbally there is very general agreement; for both the general run of men and people of superior refinement say that it is happiness, and identify living well and doing well with being happy. But with regard to what happiness is they differ... and often even the same

man identifies it with different things, with health when he is ill, with wealth when he is poor” “Shall we not, like archers who have a mark to aim at, be more likely to hit upon what is right?” (2). So in this primary sense, ethics must not be understood as a mere set of norms of what you should not do. Negative norms are in the interest of their positive sense, which is to allow all women and men to be respected in their dignity, liberties and values to develop a flourishing life. This is what I try to reflect with my students in medicine who *prima facie* have a concept of ethics as something that restricts life and liberty.

Potter's view of the sense of contemporary life is conditioned by new circumstances and crises of a modern world that is very different from the world in Aristotle's time. Potter is concerned with the conditions for human survival and the improvement of the quality of life, with a special responsibility for the future. But I think we can find a meeting point with Aristotle when Potter states in his bioethical creed: “*I affirm my veneration for life, my believe in brotherhood of man, and my belief that I have an obligation to future generations of Man*” (1). This statement can be understood as another way to express what constitutes a “good life”.

From this perspective, a first ethical approach to regenerative medicine and stem cell research is that they are

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positive for the promotion of a good life, and a promise for the future generation.

Expectations and accomplishments in stem cell research and its ethical perspectives

In recent decades stem cell research has opened new and vast horizons of knowledge through milestone discoveries that have advanced our understanding of many complex processes in the development of life, as well as the hope of effective new treatments for many as yet incurable diseases and thus commanded extraordinary public attention. A new form of transplantation that can replace or improve injured or degenerative tissues represents a turning point in medicine (3). It is probably the most promising component for regenerative medicine, the importance of which has fueled great expectations in the media and the public. This evokes the myth of Prometheus. Some have recalled him in a romantic way as the great hero of regenerative medicine, defying the gods and the death they would impose on us poor mortals (4).

Ethical perspectives

Proposals for obtaining pluripotent cells without destroying embryos

But research in Stem Cells also presents complex ethical issues. The main ethical objection is that Embryonic Stem Cells are obtained mainly from surplus embryos from *in vitro* fertilization (IVF), which entails their destruction (5). Today, with the advances of biology, the debate of the moral status of the human embryo has turned into a philosophical one. Modern biology has shown that a new organism begins at fertilization. Already in the 19th century, Ernst Haeckel described this process as follows: (quote) "The fertilized cell is quite another thing from the unfertilized cell." "For if we must regard the spermia as real cells no less than the ova, and the process of conception as the coalescence of the two, we must consider the resultant cell as a quite new and independent organism." "The actual blending of the two cells produces a third cell, which is the germ of the child, or the new organism conceived." "Every organic individual is at first a simple cell, and as such an elementary organism, or a unit of individuality" (6). This has been confirmed by modern biology (7, 8). Logically, a human organism is a human being. Consequently, the debate is about the moral status of a human being at this stage of development, with its corresponding basic rights. I will not address the discussion about this issue, but only verify that the ethical debate ex-

ists and that for many people, governments and legislatures it is not acceptable to use human embryos for this or other purposes. It is in this context that different efforts have been made to obtain embryonic stem cells (ESC) with methods that do not imply risks to or destruction of human embryos. I will briefly mention the proposed methods and their main ethical implications. We have addressed them in detail in a recent publication (9).

Embryo biopsy: One or more blastomeres are removed from a living embryo, as is done in genetic preimplantation diagnosis. ESC lines have been obtained with this technique from animals and humans (10). The risks for the embryo of removing a blastomere are unknown, and the embryo receives no benefit from the procedure. Because of this, some authors of this technique recommend that it not be applied, except when a genetic preimplantation diagnosis is necessary. However, this raises the problem of increasing the risk for the viability of the embryo by removing two blastomeres (11).

ESC obtained from "dead" embryos: This strategy has been considered problematic because of the difficulty in having a precise criterion for death of an embryo and the final quality of the ESC derived from it (12). Is an arrested embryo dead (13)? The proposal is derived to encourage the use of poor quality embryos. An imprecise definition of embryonic death has led to the proposal to use embryos that are not considered viable, and finally poor quality embryos. This changes the original objective of avoiding the destruction of embryos since it is clear that not all the poor quality embryos that are discarded are dead.

ESC has been produced from parthenogenetic blastocyst in animals and humans (14): ESC lines have been derived from animal and human parthenotes. This is an interesting strategy. Scientists have raised concerns about the risk of not having parental imprinting, the possible negative genetic consequences if the ESC lines are homozygous and their efficiency and stability (15). From an ethical perspective, the question has been asked whether or not a parthenote blastocyst is an altered human embryo or just a ball of cells without organization. In my opinion, it is difficult to see how this doubt will be resolved (19). It is known that in several mammalian species parthenogenetic embryos can be implanted but they die around mid-gestation (16).

Altered nuclear transfer (ANT) and oocyte assisted reprogramming (OAR): This consists of a pre-emptive genetic and epigenetic modification of the nucleus of the somatic cell to be transferred and an alteration of the oocyte cytoplasm before nuclear transfer is done. This strategy

pretends to bypasses the embryo stage and goes directly to obtaining ESC (17).

ESC was obtained by Meissner and Jaenisch in 2006 by silencing the *Cdx* gene in somatic cell nuclear transfer to the oocyte. But these authors indicate that “because the *Cdx2*-deficient embryo is not obviously abnormal before the onset of *Cdx2* expression, this approach may not solve the ethical dilemma” (18). In view of the new strategies for obtaining pluripotent stem cells, in my judgment this approach is now outdated.

Other ethical issues common to all stem cell research

Independent of the ethical problem of using human embryos for obtaining stem cells, there are other ethical problems emerging with stem cells. Most of them are centered on the clinical use of stem cells. It is generally assumed that the only scientifically and ethical route to achieve new medical treatments is through approved clinical trials. However, there is discussion about whether innovation in medicine can only work through clinical trials and what would be the conditions for accepting this exception from a scientifically and ethical view (19, 20). This is a hot topic for scientist, the media and legislators. As well, it must be pointed out that the shift to clinics has additional aspects particular to stem cells, such as informed consent, intellectual property, downstream research, financial and nonfinancial conflicts of interest (21). But probably one of the most alarming ethical concerns today is the increasing offer of SC treatment by many clinics without regulation, which exploits patients with incurable diseases and discredits serious stem cell research. The need for regulating treatments outside of research protocols is urgent. The problem has been addressed by scientist, bioethicists and scientific societies that have provided guidelines to researchers, care givers and patients (22, 23). It seems that in the near future it will be necessary to establish global regulations, which implies agreements among countries to effectively protect patients and ensure the proper use of the impressive developments that we can expect to achieve in treatment and research with SC (24).

Recent advances in stem cell research

Direct epigenetic reprogramming of somatic cells to induce pluripotent cells (iPS)

A spectacular breakthrough was made in the field of stem cells when Takahashi and Yamanaka discovered that viral transfection of four transcription factor genes in somatic cells induce the production of ESC-like pluripotent

stem cells (iPS) (25). Since the publication of their article, an impressive amount of research has been done confirming the discovery and making significant progress in solving some of the problems pointed out by Takahashi and Yamanaka. IPS are similar to ESC in morphology, proliferation, and gene expression (26, 27). The generation of viable chimeras was the strongest proof of their similarity to ESC. Because it is possible to use a patient’s own somatic cells to generate therapeutic iPS cells, they hold the great promise of generating patient-specific cell types for cell replacement therapy, eliminating the risk of rejection. Treatment of Parkinson and of sickle cell anemia with iPS in rats has produced improvements in these diseases (28, 29).

From an ethical perspective, the reprogramming of somatic cells to obtain iPS bypasses the major problems involved in obtaining and using ESC. There is no destruction or manipulation of the embryo, nor the need for oocytes. Its potential in the treatment of a host of diseases in different areas of medicine opens the possibility for the first time of a consensus between scientists, and ethicists with different anthropological and ethical views. Ian Wilmut stated that it is “easier to accept socially” and so decided not to pursue his license to clone human embryos because this newer technique has more potential for regenerative medicine (30).

Some scientist and philosophers have argued that research with iPS does not circumvent the ethical problems related to ESC. They point out that the knowledge obtained with ESC has been used in iPS research and that to assess the pluripotent profile of iPS cells, it is necessary to compare it to the ESC profile. It has also been argued that for these reasons new lines of ESC are needed (31, 32). We think that these are extrinsic relationship to iPS. This does not entail the continued production of ESC and the destruction of embryos. Most new drugs and treatments have been tested in animal studies without the use of a human organism. If preclinical studies demonstrate a reasonable benefit and safety, the shift to clinical trials will be acceptable in the classical phases universally approved by the scientific community. But it must be acknowledged that the shift of SC to the clinical setting has more limitations than in the case of drugs because extrapolating results from animal studies to humans is more complex due to the unpredictability of cell behavior in a different environment. Thus, clinical trials must be carefully designed. The results of such studies in the end will be proof of the safety and efficacy of iPS and provide the definitive answer to unresolved questions.

The great interest in iPS is evidenced by the increasing

number of articles one can find in a Pubmed. From only one article in 2006, there have been more than four hundred published in 2010.

However, as Professor Yamanaka points out, "The potential of iPS cell technology is enormous, but this technology is still in its infancy" (33). Researchers are aware that there are still major difficulties to be surmounted before using reprogrammed cells for therapeutic applications in humans (34):

- The potentially harmful effects involved in the use of retroviral vector for introducing ectopic genes: Many different strategies are being evaluated, such as the use of fewer factors, other viruses, plasmids, transposons and chemicals. An interesting advance is the induction of iPS by protein-cell reprogramming without genetic manipulation in somatic cells (35).
- The production of teratomas: iPS, like ESC, can produce teratomas when implanted under the skin. Before advancing to therapeutic applications, it will be necessary to clearly demonstrate that differentiated iPS cells do not produce tumors in hosts. Despite the production of iPS without the c-myc gene (36), the problem has not been resolved entirely.
- The low efficiency in the reprogramming technique: Recently, the reprogramming of bone marrow cells has proven to be more efficient than from mouse fibroblasts.
- Finally there is the challenge to progress in generating human iPS and the need to develop consistent differentiation procedures to allow its use in regenerative medicine. There is also the question of whether or not all iPS cell clones attain complete nuclear reprogramming.

All these problems are subject to intense research. It is plausible that these technical problems can be overcome and allow the application of iPS to regenerative medicine in humans. This would overcome the problem of using embryos or eggs and the threat of immune rejection.

Direct fate conversion of somatic cells to tissue specific cells

This form of transdifferentiation has been taken up with renewed interest with the advent of somatic reprogramming. Recently, fibroblast has been successfully reprogrammed directly to neural cells and cardiomyocytes (37) and direct conversion of fibroblasts to functional neurons by defined Factors (38). This form of reprogramming circumvents the pluripotent stage. These new technologies have the advantage of avoiding the formation of tumors and other problems mentioned earlier, and could

eventually substitute existing technologies for generating iPS cells and ES cells for use in regenerative medicine.

Science and human values: Bridge to the future

Van Raessler Potter stated: "Mankind is urgently in need of a new wisdom that will provide <knowledge of how to use knowledge> for man's survival and for improvement in the quality of life" (1).

The UNESCO Universal Declaration on Bioethics and Human Rights embodies the ideas expressed by Potter: "Recognizing that, based on the freedom of science and research, scientific and technological developments have been, and can be, of great benefit to humankind in increasing inter alia life expectancy and improving quality of life, and emphasizing that such developments should always seek to promote the welfare of individuals, families, groups or communities and humankind as a whole in the recognition of the dignity of the human person and the universal respect for, and observance of human rights and fundamental freedoms" (39).

The Greeks also asked a more specific, ever-present question: the question about human beings. The Oracle at Delphi bears the inscription: "*Man, know thyself*". This is a response to the question: What is man? An existential, rather than theoretical, question that has come down to us through the centuries in different forms. Who am I? What is the meaning of my life? Today such questions are even more relentless and at times full of contradictions and anguish. With the progress in science and technology, especially in life sciences, the question has acquired a new dimension and an urgent need for the future of mankind. Potter specifies his position stating that "the two most important ingredients in achieving the new wisdom (which he called bioethics) that is so desperately needed are: biological knowledge and human values". We could also say human goods. Ethics, as I stated at the beginning, has first a positive conception, to promote a good and flourishing life. One could say that everybody looks for happiness and this is related to the pursuit of human goods. Undoubtedly health is a human good and regenerative medicine is a great promise for better health. But as the World Health Organization points out: "Health is not the objective of living" (40), rather it is an instrument to a good, and not an end in itself. Being in good health allows one to access other human values and goods that make life flourish. Among these are the power to learn and to know, to work and play, the enjoyment of art and beauty, especially the delight of friendship, solidarity and love. Thus love and respect for each other and for the environment represent an integration of the ideas of many philosophers, scientists

and humanists who are aware of the need to have a global approach to the care of personal dignity, life and what we can call natural and human environments.

Final comments

I would like to summarize these reflections with the wise words and life experience of Mother Theresa of Calcutta:

“We can cure physical diseases with medicine, but the only cure for loneliness, despair, and hopelessness is love. There are many in the world who are dying for a piece of bread, but there are many more dying for a little love” (www.great-quotes.com/quote/1374977).

In a similar perspective, Potter’s grandson, Josh Simon wrote the following poem for the memorial service for Van Rensselaer Potter held on November 7, 2001 (www.harvard-squarelibrary.org/unitarians/potter.html).

To Save the Earth

We must First Love
Respecting Life
and each other
now in the Present
We Exist
for the Future
generations of Humanity
We must care
We shall
Live on this Earth
We Should Survive.

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Potential conflict of interest

The authors have no conflicting financial interest.

References

- Potter VR. Bioethics: Bridge to the Future. Englewood Cliffs, NJ: Prentice-Hall; 1971
- Aristotle, Nicomachean ethics. Responsibility: Aristotle; translated by W. D. Ross. Nicomachean ethics/Aristotle.; W D Ross; Lexington, KY: World Library Classics; 2009
- Helmy KY, Patel SA, Silverio K, Pliner L, Rameshwar P. Stem cells and regenerative medicine: accomplishments to date and future promise. *Ther Deliv* 2010;1:693-705
- Rosenthal N. Prometheus's vulture and the stem-cell promise. *N Engl J Med* 2003;349:267-274
- Faggioni MP. Anthropological and ethical reflections on the production and use of embryonic stem cells. *Cell Prolif* 2008;41 Suppl 1:71-77
- Haeckel E. The evolution of man. Vol. 1. London: WATTS & CO; 1912.53-54. Online version: <http://www.gutenberg.org/ebooks/8700>
- Gilbert SF. Fertilization: Beginning of a new organism. Chapter 7. In: Gilbert SF, editor. *Developmental Biology*. 8th ed. Sunderland, MA: Sinauer Associates Inc; 2006. 175-210
- Lodish H. Life begins with cells. Chapter 1. In: Lodish H, Berk A, Matsudaira P, Kaiser CA, Krieger M, Scott P, Zipursky L, Darnell J, editor. *Molecular Cell Biology*. 6th ed. New York, NY: W.H. Freeman & Company; 2008
- Ventura-Juncá P, Santos M, Larraín J. Proposals for embryonic stem cell production without destroying human embryos: scientific and bioethical challenges. *Acta Bioethica* 2009;15:222-233
- Klimanskaya I, Chung Y, Becker S, Lu SJ, Lanza R. Human embryonic stem cell lines derived from single blastomeres. *Nature* 2006;444:481-485
- Simpson JL. Medicine: blastomeres and stem cells. *Nature* 2006;444:432-435
- Landry DW, Zucker HA, Sauer MV, Reznik M, Wiebe L. Hypocellularity and absence of compaction as criteria for embryonic death. *Regen Med* 2006;1:367-371
- Zhang X, Stojkovic P, Przyborski S, Cooke M, Armstrong L, Lako M, Stojkovic M. Derivation of human embryonic stem cells from developing and arrested embryos. *Stem Cells* 2006;24:2669-2676
- Kim K, Lerou P, Yabuuchi A, Lengerke C, Ng K, West J, Kirby A, Daly MJ, Daley GQ. Histocompatible embryonic stem cells by parthenogenesis. *Science* 2007;315:482-486
- Brevini TA, Pennarossa G, deEguileor M, Tettamanti G, Ragni G, Paffoni A, Gandolfi F. Parthenogenetic cell lines: an unstable equilibrium between pluripotency and malignant transformation. *Curr Pharm Biotechnol* 2011;12:206-212
- Sturm KS, Flannery ML, Pedersen RA. Abnormal development of embryonic and extraembryonic cell lineages in parthenogenetic mouse embryos. *Dev Dyn* 1994;201:11-28
- Arkes H, Austriaco NP, Berg T, Brugger EC, Cameron NM, Capizzi J, Condit ML, Condit SB, FitzGerald KT, Flannery K, Furton EJ, George RP, George T, Gomez-Lobo A, Grisez G, Grompe M, Haas JM, Hamerton-Kelly R, Harvey JC, Hoehner PJ, Hurlbut WB, Kilner JF, Lee P, May WE, Miranda G, Mitchell CB, Myers JJ, Oleson C, Pacholczyk T, Ryan PF, Saunders WL, Stevens D, Swetland SW,

1. Potter VR. Bioethics: Bridge to the Future. Englewood

- Whelan ME, Williams T. Production of pluripotent stem cells by oocyte-assisted reprogramming: joint statement with signatories. *Natl Cathol Bioeth Q* 2005;5:579-583
18. Meissner A, Jaenisch R. Generation of nuclear transfer-derived pluripotent ES cells from cloned Cdx2-deficient blastocysts. *Nature* 2006;439:212-215
 19. Lindvall O, Hyun I. Medical innovation versus stem cell tourism. *Science* 2009;324:1664-1665
 20. Hyun I. Allowing innovative stem cell-based therapies outside of clinical trials: ethical and policy challenges. *J Law Med Ethics* 2010;38:277-285
 21. Lo B, Parham L. Ethical issues in stem cell research. *Endocr Rev* 2009;30:204-213
 22. Lau D, Ogbogu U, Taylor B, Stafinski T, Menon D, Caulfield T. Stem cell clinics online: the direct-to-consumer portrayal of stem cell medicine. *Cell Stem Cell* 2008;3:591-594
 23. Hyun I, Lindvall O, Ahrlund-Richter L, Cattaneo E, Cavazzana-Calvo M, Cossu G, De Luca M, Fox IJ, Gerstle C, Goldstein RA, Hermerén G, High KA, Kim HO, Lee HP, Levy-Lahad E, Li L, Lo B, Marshak DR, McNab A, Munsie M, Nakauchi H, Rao M, Rooke HM, Valles CS, Srivastava A, Sugarman J, Taylor PL, Veiga A, Wong AL, Zoloth L, Daley GQ. New ISSCR guidelines underscore major principles for responsible translational stem cell research. *Cell Stem Cell* 2008;3:607-609
 24. Shalev C. Stem cell tourism--a challenge for trans-national governance. *Am J Bioeth* 2010;10:40-42
 25. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* 2006;126:663-676
 26. Wernig M, Meissner A, Foreman R, Brambrink T, Ku M, Hochedlinger K, Bernstein BE, Jaenisch R. In vitro reprogramming of fibroblasts into a pluripotent ES-cell-like state. *Nature* 2007;448:318-324
 27. Dick E, Matsa E, Bispham J, Reza M, Guglieri M, Staniforth A, Watson S, Kumari R, Lochmüller H, Young L, Darling D, Denning C. Two new protocols to enhance the production and isolation of human induced pluripotent stem cell lines. *Stem Cell Res* 2011;6:158-167
 28. Hanna J, Wernig M, Markoulaki S, Sun CW, Meissner A, Cassady JP, Beard C, Brambrink T, Wu LC, Townes TM, Jaenisch R. Treatment of sickle cell anemia mouse model with iPS cells generated from autologous skin. *Science* 2007;318:1920-1923
 29. Wernig M, Zhao JP, Pruszak J, Hedlund E, Fu D, Soldner F, Broccoli V, Constantine-Paton M, Isacson O, Jaenisch R. Neurons derived from reprogrammed fibroblasts functionally integrate into the fetal brain and improve symptoms of rats with Parkinson's disease. *Proc Natl Acad Sci U S A* 2008;105:5856-5861
 30. Wilmut I. The first direct reprogramming of adult human fibroblasts. *Cell Stem Cell* 2007;1:593-594
 31. Brown MT. Moral complicity in induced pluripotent stem cell research. *Kennedy Inst Ethics J* 2009;19:1-22.
 32. Watt JC, Kobayashi NR. The bioethics of human pluripotent stem cells: will induced pluripotent stem cells end the debate? *Open Stem Cell J* 2010;2:18-24
 33. Yamanaka S. A fresh look at iPS cells. *Cell* 2009;137:13-17
 34. Hanna JH, Saha K, Jaenisch R. Pluripotency and cellular reprogramming: facts, hypotheses, unresolved issues. *Cell* 2010;143:508-525
 35. Cho HJ, Lee CS, Kwon YW, Paek JS, Lee SH, Hur J, Lee EJ, Roh TY, Chu IS, Leem SH, Kim Y, Kang HJ, Park YB, Kim HS. Induction of pluripotent stem cells from adult somatic cells by protein-based reprogramming without genetic manipulation. *Blood* 2010;116:386-395
 36. Nakagawa M, Koyanagi M, Tanabe K, Takahashi K, Ichisaka T, Aoi T, Okita K, Mochiduki Y, Takizawa N, Yamanaka S. Generation of induced pluripotent stem cells without Myc from mouse and human fibroblasts. *Nat Biotechnol* 2008;26:101-106
 37. Ieda M, Fu JD, Delgado-Olguin P, Vedantham V, Hayashi Y, Bruneau BG, Srivastava D. Direct reprogramming of fibroblasts into functional cardiomyocytes by defined factors. *Cell* 2010;142:375-386
 38. Vierbuchen T, Ostermeier A, Pang ZP, Kokubu Y, Südhof TC, Wernig M. Direct conversion of fibroblasts to functional neurons by defined factors. *Nature* 2010;463:1035-1041
 39. UNESCO adopts Universal Declaration on Bioethics and Human Rights. 20 October 2005
 40. WHO/HPR/HEP/95.1. The First International Conference on Health Promotion. Ottawa, 21 November 1986