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TRUTH IN SCIENCE AND MEDICINE
THE HOPE AND HYPE OF STEM CELL THERAPIES

Abstract

The article examines the practice of cell therapies, often named as stem cell therapies. For the general public this is recognized as promising treatment for many diseases, offering hope for many people to restore health to themselves or their loved ones. However, despite the enormous potential that this type of treatment holds, it has its limitations. The tension between hope, science, truth and deception can come to the fore especially when someone is fighting for their life. Moral and ethical issues play a key role in such cases, serving as guide-posts obscured, however, by information noise.

Keywords: stem cell therapy, science, medicine, communication

We live in a time when science is enjoying unprecedented success. Science has proven that its methodology is correct; it has the power to uncover truths about the world, and it has demonstrated that scientific knowledge can be used in practical situations. Thanks to science, we can travel around the world, flying in planes weighing hundreds of tons. Thanks to science, human beings were able to travel to the Moon and return safely back to Earth. Understanding biological mechanisms has allowed scientists to demonstrate that diseases have a natural origin, enabling scientists to develop effective methods for their diagnosis and treatment. Science has not only allowed us to cure diseases, but also prevent some of them. Thanks to science, and the introduction of vaccines, antibiotics and improved living conditions, the rate of child mortality has dropped significantly. Although,

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of course, things still need to improve in many regions of the world, one can see the significant progress that has been made in the last 50 years.

Humans can fly from continent to continent, and even into space. Humans can treat diseases by acting effectively against disrupted biological processes. This can only be done through science. No religion is effective. No prayers of billions of believers can move a heavy object from the ground; no miracle healing happens because of faith.

However, in a time when everyone is dependent on science and its products, the truth of science is facing attacks from various sides. Paradoxically, despite still underestimating the significance and power of science, people expect miracles to happen, particularly in the field of biomedical science. People expect medicine to cure all diseases. However, concomitantly, there is a common lack of knowledge and misunderstanding of biological processes. Despite the effectiveness of vaccines, the anti-vaccine movement is growing, dispersing fake news about their side effects, including dubious claims that they cause autism. Europeans, in particular, are suspicious about the alleged dangers of plant genetic modification. Sociological pools demonstrate not-so-rare irrational beliefs that "natural" organisms do not contain genes, in contrast to genetically modified ones. Supporters of so-called natural products boost the enormous market of food supplements, claiming that they have miraculous effects on every real (as well as fake) health problem.

People want to live longer, stay young longer, and they want a cure for every disease. People are looking for a miracle and are reluctant to accept the truth. This is because the truth can often be harsh. We still don't have a cure for every disease; many treatments are ineffective, and even effective treatments can cause unpleasant and sometimes dangerous side-effects. People desperately look for hope. This is their right, particularly for severely sick patients or the parents of sick children. They search the internet and look for miracle treatments, and often find… hype.

As in other forms of social activity, it's no different in science and medicine. One can find many who claim to possess the answers to our problems, that they have miracles within arm's reach. Like populist politicians who claim they have the answer to every social problem, like priests offering eternal salvation, there are populist scientists and physicians who claim they have a cure for almost every health problem. They have stem cells. Like populists who claim that everything is very easy to achieve, populist physicians and scientists say that stem cells are the way to treat incurable diseases – particularly,

so-called adult stem cells which, they claim, can be isolated from tissues such as fat, or from the remnants of childbirth, namely the umbilical cord. Moreover, their application appears to be very easy and safe. However, I would like to give some examples of how this actually works.

Stem cells are cells which can self-renew, generating other stem cells by cell division, and which can differentiate into specialized cell types (Blau and Daley 2019). However, there is no one group of stem cells, and different stem cells have different properties. There are cells which are totipotent, which can create a whole organism, and these are zygotes or the first blastomeres being the result of a zygote's cell division. There are pluripotent cells, such as embryonic stem cells, which are derivatives of the inner cell mass of an early embryo (blastocyst) and which can be cultured in the laboratory practically indefinitely. Although pluripotent cells can indeed differentiate into almost every cell type of the human body, except the trophoblast (which contributes to the placenta), they cannot create a whole organism. In our organs, as in bone marrow, we have multipotent stem cells which can differentiate into many cell types but only of one given group. While hematopoietic stem cells from the bone marrow can differentiate into every blood cell type, they cannot form bone. On the other hand, in bone marrow there are skeletal stem cells (named mesenchymal stem cells) which can form chondrocytes, adipose cells and bone – but not blood cells. Finally, we have unipotent stem cells, such as, for example, certain cells in the skin or the satellite cells in our muscles, which can differentiate into the cells of a given tissue: the epidermis or the skeletal muscles, respectively.

Stem cells are very effective and really powerful. From each zygote more than 200 different cell types can be created. A whole human body consists of more than 10^{12} cells. Hematopoietic stem cells (HSCs) in our bone marrow regenerate blood, giving rise to 200 billion red blood cells, 10 billion white blood cells, and 400 billion platelets every day. HSCs can save lives because they can be used to treat blood disorders such as leukemia, anemia or immune deficiencies. They can be harvested from the bone marrow or mobilized to the donor's blood, collected and injected into the patient in need. These treatments are very efficient and have saved the lives of hundreds of thousands of people. Of course, as they still need refinement, scientists are still looking for ways to improve methods of HSC mobilization. For example, in our recent study we described new way of HSC mobilization to the blood of experimental mice (Szade et al. 2020).

Of course, before any application in human beings, such an approach has to be carefully tested in order to ensure it is safe and effective.

We have stem cells in different organs of our body. We have stem cells in certain parts of the brain, but not in every region of it. We have stem cells which regenerate our skin. We have stem cells which constantly repair the internal lining (epithelium) of our intestines. We have satellite cells which regenerate our muscles. We have stem cells in the bone marrow, regenerating our blood (HSCs) and skeletal stem cells, which can regenerate our bones. When a child is born, some blood can be collected from the umbilical cord and this umbilical cord blood contains HSCs, as in bone marrow, and can be used for the treatment of blood diseases (but not in the same child!). Stem cells are thus used to regenerate the corneal epithelium of the eye, regenerate blood in hematopoietic diseases or regenerate skin.

Recently, a combination of stem cell therapy with gene therapy has allowed scientists to treat diseases that have until now been incurable, such as severe combined immunodeficiency syndromes (SCIDs) – when a child is born without an immune system and there is a danger of dying from infections that would normally not be harmful. One example of such a SCID is adenosine deaminase immunodeficiency (ADA). The Italian scientists and physicians have developed a method for its treatment, named Strimvelis, which since 2016 has been registered by the European Medicines Agency. Strimvelis combines gene and cell therapy. A sick child's stem cells, which are not able to differentiate efficiently into various blood cells, are isolated from the patient's bone marrow and modified *in vitro* with the correct ADA gene that is missing in the patient. Then these engineered stem cells are reinfused back into the patient in order to restore their immune system. Strimvelis is really safe and effective for patients with ADA-SCID (De Luca et al. 2019)

Skin stem cells can help regenerate our skin. However, they cannot always do it effectively; for example, when there is extensive skin damage due to severe burns. At the same time, in such a case skin stem cells can be isolated from the part of the skin that is not damaged; they can be multiplied in the laboratory and differentiated into epidermal keratinocytes which can then be applied to the damaged areas.

In 2015 the European Medicines Agency registered Holoclar, which is a method used to regenerate a damaged corneal epithelium using a patient's own limbal stem cells. When the cornea is damaged, for example,

by chemicals, it can result in the loss of sight. However, if the limbal stem cells, namely the stem cells which normally regenerate the corneal epithelium, are not fully destroyed, they can be taken from the eye, multiplied in the laboratory, and the obtained cornea epithelium can be injected back into the eye of the patient (De Luca et al. 2019).

The potential of epidermal stem cells to regenerate damaged skin has been recently demonstrated in a joint effort of German physicians and Italian scientists who saved the life of a Syrian boy severely suffering from junctional epidermolysis bullosa (EB), a devastating terminal disease. As this boy does not have the correct laminin 332 gene, he lacks this protein that is required for the proper functioning of the skin. In EB, the skin of patients is severely damaged, as in this boy, who lost almost 60% of his total body protective surface. To save his life, which was threatened by repeated sepsis, the researchers took a piece of undamaged skin, isolated the stem cells, introduced the proper gene into these stem cells and multiplied and then differentiated them, generating skin epidermis, which they applied to the damaged body of the patient. In this way they saved the life of the boy who can now lead a normal life (De Luca et al. 2019).

To summarize, stem cells from the bone marrow which contain HSCs can be used to treat blood diseases. Epidermal stem cells can be used to regenerate skin. Limbal stem cells in the eye can regenerate the corneal epithelium. However, some even claim that HSCs or so-called mesenchymal stem cells can be used to treat any organ imaginable, not only to regenerate the blood, but also to regenerate muscles, the skin, heart, liver and even the nervous system (for references see: Dulak et al. 2015, Langrzyk et al. 2018). Moreover, even at websites such as the American registry of clinical trials[2], one can find an enormous list of diseases which are claimed be treated with stem cells isolated from the bone marrow or other sources.

Nevertheless, there is a lack of convincing evidence on the application of one type of cell for the treatment of so many unrelated diseases. Although supporters state that there are numerous studies used to prove that these cells are effective, there are also serious concerns over the integrity of this research.

But why does this happen? The simplest answer is that stem cells are considered as a cure-all. The supporters claim that stem cells can be

[2] See: https://clinicaltrials.gov/.

isolated from bone marrow, fat, teeth, menstrual blood or Wharton jelly (the gelatinous substance within the umbilical cord which is discarded after delivery). There are many clinics which claim that cells isolated from such tissues can be used to treat almost anything. There is a growing problem of unregulated, so-called stem cell therapies, which has led to stem cell tourism. This not only includes the United States and Asian countries but is happening in Poland as well. A search online brings up a list of different commercial institutions offering treatments for a host of diseases. These clinics charge sometimes an enormous amount of money for such a "treatment". Clinic websites list diseases such as cerebral palsy, autism, amyotrophic lateral sclerosis, muscular dystrophies or different forms of blindness. They claim they can be treated with cells of the same cell type, isolated from the umbilical cord or cord blood. These cells, coming from unrelated donors, are injected into patients' blood, spinal cord or the eye in hopes of curing patients (Sipp et al. 2017, Srivastava 2019).

One cell type for every disease. A miraculous treatment for everything. Why is this dubious? Firstly, different diseases have different backgrounds and origins, and many are not linked to cell loss that would require cell replacement with stem cells. As diseases affect different organs, it warrants the question as to why cells are isolated from unrelated organs, with functions that are not well known and not even proven to be stem cells, being used to treat these diseases.

Reports on the effectiveness of such treatments are doubtful. They include so-called medical experiments that are often performed without scientific and medical scrutiny. There is no control group, no placebo. There is a lack of careful monitoring of patients and objective testing to confirm these treatments are effective. There is a lack of independent assessments by professional reviewers. Results are not published in peer-reviewed journals, and if they are, the quality of these papers and journals are often poor. We have to be aware, that as in the traditional press, there are respectable journals and there are tabloids and a lot in between. Moreover, the claims concerning the effectiveness of such commercial treatments are also based on personal, unverified patient statements.

The suggestions that the same cell can be used to treat everything sounds like the Holy Grail, a "natural" miracle treatment for every condition. Looking back, one can find that this was started when the potential of embryonic stem cells (ESC), which indeed can differentiate to many cell types, was recognized, and hope for the treatment of incurable diseases

began to grow. However, reluctance and ethical objections to using ESC, due to the fact that obtaining them requires destroying the embryo, directed interest to adult stem cells, with the belief that they can do the same as ESC. Unfortunately, they cannot, a fact that has been convincingly demonstrated. Perpetuating the claims on the pluripotency or multipotency of adult stem cells indicates also that there is insufficient knowledge and a lack of understanding of biological mechanisms, stem cell properties and their real potential.

Stem cell treatment sounds like a simple solution for everything and everyone. This is like populism or religion. Populism or religions do not need evidence. Populism relies on emotions and beliefs; the same is true for religion. Strange as it may seem, apparently, the problem of populism can also be found in science and medicine. The chaplains of such beliefs have straight and simple messages. They recognize the needs of others, saying that people have the right to try them out, that stem cells have to be applied quickly and that there is no need for prolonged research. They are vocal in making accusations that the rules of registering new drug treatments are dictated by soulless regulatory agencies which prevent the introduction of promising treatments for desperate patients.

Although this may sound surprising, this is the basis of the arguments often used by clinics which offer such unjustified therapies. Populism is reciprocal: there are patients in need and there are those who can fulfill such a need. Physicians who offer these types of treatments, the brave and generous, are eager to fulfill the wishes of ordinary people.

One can ask: where is the problem in this? If stem cells work in some cases, why shouldn't they work in others? Why are we so afraid? Firstly, treatment has to be evidence-based. In modern medicine treatment cannot be offered on the basis of just beliefs, with no support from rigorously performed preclinical and clinical research. We also should react because there are serious side effects that come with this type of cell therapy (Daley 2017, Marks et al. 2017, Mummery et al. 2014). People have lost their sight after being injected with cells isolated from fat; some patients developed a tumor at the site of injection of unknown "stem cells," and some patients have even lost their lives. It is also assumed that many people who make a decision to go ahead with unregistered therapies do not report side effects. Therefore, the International Society for Stem Cell Research (ISSCR), the largest professional organization of scientists working on stem cells, have warned about the dangers of unproven stem cell-based intervention

(*ISSCR 2016*). This was done in 2016 when the first guidelines on this issue were released. Moreover, this was repeated in June 2019 and May 2021 as there are still problems with clinics that offer unjustified therapies. Recently, in spring 2020, a serious warning was issued by the Committee of Advanced Therapies of the European Medicines Agency (*EMA* 2020) and from the European Academies' Science Advisory Council (EASAC) (*EASAC* 2020).

At the same time, despite the pessimistic messages and warnings of the risks, there is reasonable optimism. Stem cells have great potential and can be used for therapies – however, they must use real, not fake "stem" cells. Moreover, their application should not be rushed at the expense of basic research and without at least a basic understanding of stem cell properties and the mechanism of their actions. The potential of stem cell therapy is immense and its application extends beyond regenerative medicine. However, even with such promising approaches, the old medical principle, *primum non nocere*, should be considered first of all.

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BIBLIOGRAPHY

Blau H.M., Daley G.Q. 2019. Stem Cells in the Treatment of Disease, *The New England Journal of Medicine*, 380(18), 1748–1760. https://doi.org/10.1056/NEJMra1716145.

EMA Warns Against Using Unproven Cell-Based Therapies. 2020, April 28. *European Medicines Agency*. Retrieved from: https://www.ema.europa.eu/en/documents/public-statement/ema-warns-against-using-unproven-cell-based-therapies_en.pdf.

Główny Inspektorat Farmaceutyczny. 2020, May 5. Ostrzeżenie EMA przed stosowaniem niepotwierdzonych terapii komórkowych. Retrieved from: https://www.gov.pl/web/gif/ostrzezenie-ema-przed-stosowaniem-niepotwierdzonych-terapii-komorkowych.

Daley G.Q. 2017. Polar Extremes in the Clinical Use of Stem Cells, *The New England Journal of Medicine*, 376(11), 1075–1077. https://doi.org/10.1056/NEJMe1701379.

De Luca M., Aiuti A., Cossu G., Parmar M., Pellegrini G., Robey P.G. 2019. Advances in Stem Cell Research and Therapeutic Development, *Nature Cell Biology*, 21(7), 801–811. https://doi.org/10.1038/s41556-019-0344-z.

Dulak J., Szade K., Szade A., Nowak W., Józkowicz A. 2015. Adult Stem Cells: Hopes and Hypes of Regenerative Medicine, *Acta Biochimica Polonica*, 62(3), 329–37. https://doi.org/10.18388/abp.2015_1023.

EASAC report: Challenges and potential in regenerative medicine. 2nd June 2020, no. 40. Retrieved from: https://easac.eu/publications/details/challenges-and-potential-in-regenerative-medicine/.

Polska Akademia Nauk. 2020, June 2. Akademie nauk ostrzegają przed „cudownymi" terapiami komórkami macierzystymi. Retrieved from: https://informacje.pan.pl/index.php/informacje/materialy-dla-prasy/3026-akademie-nauk-ostrzegaja-przed-cudownymi-terapiami-komorkami-macierzystymi.

https://clinicaltrials.gov/

International Society For Stem Cell Research. 2016 May 12. *ISSCR Guidelines for Stem Cell Science and Clinical Translation*. Retrieved from: www.isscr.org; http://www.isscr.org/docs/default-source/all-isscr-guidelines/guidelines-2016/isscr-guidelines-for-stem-cell-research-and-clinical-translationd67119731dff6ddbb37cff0000940c19.pdf?sfvrsn=4.

Langrzyk A., Nowak W.N., Stępniewski J., Jaźwa A., Florczyk-Soluch U., Józkowicz A., Dulak J. 2018 July 10. Critical View on Mesenchymal Stromal Cells in Regenerative Medicine, *Antioxidants & Redox Signaling*, 29(2), 169–190. https://doi.org/10.1089/ars.2017.7159.

Marks P. W., Witten C. M., Califf R. M. 2017 March 16. Claryfying Stem-cell Therapy's Benefits and Risks, *The New England Journal of Medicine*, 376(11), 1007–1009. https://doi.org/10.1056/NEJMp1613723.

Mummery C., van de Stolpe A., Roelen B., Clevers H. 2014. *Stem Cells. Scientific Facts and Fiction* (2nd ed.), London: Academic Press.

Sipp D. et al. 2017 July 5. Marketing of Unproven Stem Cell-based Interventions: A Call to Action, *Science Translational Medicine*, 9(397). https://doi/org/10.1126/scitranslmed.aag0426.

Srivastava D. 2019 September 4. Don't Believe Everything You Hear About Stem Cells, *Scientific American*. Retrieved from: https://blogs.scientificamerican.com/observations/dont-believe-everything-you-hear-about-stem-cells/.

Szade A. et al. 2019 December 1. Cobalt Protoporphyrin IX Increases Endogenous G-CSF and Mobilizes HSC and Granulocytes to the Blood, *EMBO Molecular Medicine*, 11(12). https://doi.org/10.15252/emmm.201809571.