Clinical applications of cell therapy

Giant Leaps for Small Cells

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Modern medicine is developing newer and newer methods of treatment, supplementing traditional medications with the latest scientific achievements. For example, sometimes special cells derived from the patient or a donor, or even created in a laboratory, can used as "medicines" in their own right

E. Donall Thomas, the father of cell therapy, was the first to successfully transplant hematopoietic stem cells, giving a bone marrow transplant to a patient with cancer disease in 1959. Such a surgery was performed in Poland for the first time in 1983 by Prof. Wiesław Jędrzejczak and Prof. Cezary Szczylik. Nowadays this method is applied not just in cancer therapy but also in the treatment of dozens of diseases, such as congenital immunodeficiencies or autoimmune and metabolic diseases.

Although bone marrow stem cells are still the subject of intensive research, a great deal of work now underway relates to somatic cells. Polish laboratories can boast of significant achievements in this respect, as the Polish researcher Prof. Moskalewski developed a method for isolating pancreatic islets as early as in the 1960s. This method, now modified, is still used today in transplants in humans. Poland's first tissue and cell banks were also established at that time.

Fulfilling the promise

Stem cells are nowadays used in virtually every medical field, ranging from skin grafts, through the regeneration of cartilage and attempts to reconstruct internal organs, to the treatment of neurological diseases or immunosuppression. These therapies make use of adult stem cells, obtained from the body after birth. Although their differentiation potential is usually limited to one specific tissue (such cells are described as "unipotent"), they are safer for the patient than cells obtained in any other way.

For some time, great enthusiasm was aroused by the possibility of using embryonic stem cells, derived from embryos, because they can differentiate into any type of tissue (they are "pluripotent"). However, researchers have failed to overcome the barrier of the tumorigenic potential of these cells – within a number of months after transplantation they may develop into life-threatening germ cell tumors called teratomas. Currently, great expectations are associated with very small embryonic-like stem cells (VSEL), recently discovered by a Polish researcher, Prof. Ratajczak. These are – to keep it very simple – embryonic tissue residues scattered throughout the body after birth. They retain the pluripotency of embryonic cells, but do not exhibit the same tumorigenic potential after transplantation. Other important avenues of research include work on induced pluripotent stem cells (IPS), which were discovered just 7 years ago but have already won their discoverers a Nobel Prize. These are somatic cells that, upon stimulation of four genes playing an important role in embryonic development, transform into embryonic cells and can give rise to any type of tissue. Both of those cell types, however, are still in the preliminary stages

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of research and needtime before they might come into use "at the patient's bedside."

Islets of success

Cell therapy also successfully uses somatic cells, which are differentiated cells of the body. The best example of this type of treatment involves the use of pancreatic islets. During a logistically complex surgery, pancreatic islets are isolated from a deceased donor and fed into the portal vein of the recipient. Then skillful immunosuppressive therapy is necessary to ensure the survival of the transplanted islets and to avoid drug-induced side effects, such as insulin resistance. Such pancreatic cell transplants serve as an excellent illustration of how modern cell therapy requires extensive collaboration between various biomedical specializations, with a successful surgical outcome hinging upon not just the work of the transplant team itself, collecting and transplanting the tissue, but also on modern immunological diagnostics, helping to choose a donor compatible with the recipient and to maintain specific conditions (i.e. a cleanroom environment), as well as the work of the team isolating the islets.

The success of pancreatic islet transplants has led other somatic cells to attract the attention of physicians and researchers. Transplantations of allogeneic hepatocytes or parathyroid cells may soon become an alternative to whole organ transplants.

Using melanoma against itself

Cancer immunotherapy is also an important field of cellular medicine. It uses immune cells capable of finding and killing tumor cells, which is used in bone marrow transplantation to treat leukemia. Initially, natural killer cells (NK) were used in cancer immunotherapy. Their function in the body is to find and kill malignant cells, but the effectiveness of such treatments was low. The next step was to apply dendritic cells (DC), which can activate the immune system and direct it to fight specific structures, including malignant cells. They recognize tumor cells based on antigens, which are specific proteins present on the cell surface. In a laboratory, DC cells can be artificially "loaded" with antigens specific to a given cancer, thus creating an anticancer cellular vaccine (the first prostate cancer vaccine

ofthis type is already on the market in the US and in Europe).

Effective immaturity

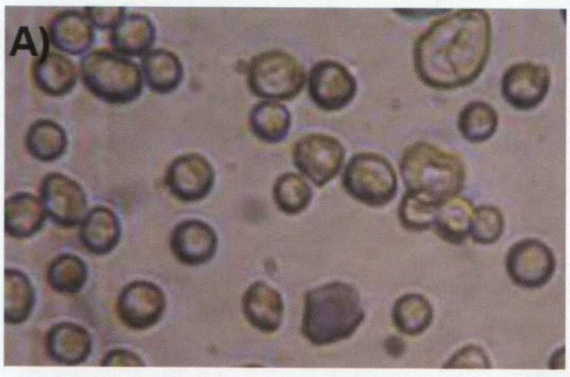
Immunosuppression is another type of cell therapy that uses several cell types, mainly DC cells, regulatory T cells (Tregs), and mesenchymal stem cells. It is used primarily to treat autoimmune diseases and to prevent transplant rejection.

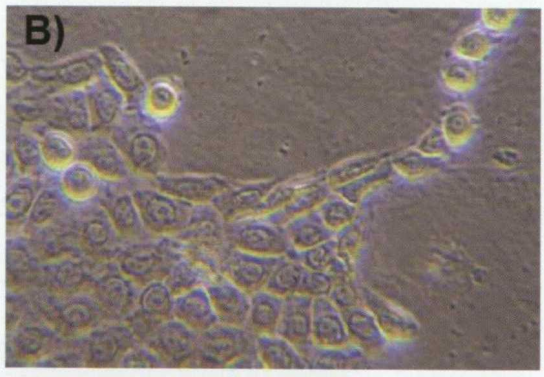
As in the case of cancer immunotherapy, immunosuppressive therapy harnesses the ability of DC cells to identify antigens and to regulate the activity of other immune system cells. However, in contrast to anticancer vaccines, where it is important to stimulate an immune response, immunosuppression works by doing just the opposite. It uses immature DCs that present antigens to autoaggressive lymphocytes but cannot activate them. As a result, the activity of these lymphocytes is significantly decreased or they even die, thus reducing the risk of an immune response against the body's own cells, which is called "autoaggressiveness." Using artificial manipulation of antigens on the DC surface, it is possible to selectively inhibit an immune response, e.g. the immune response only against the transplanted organ.

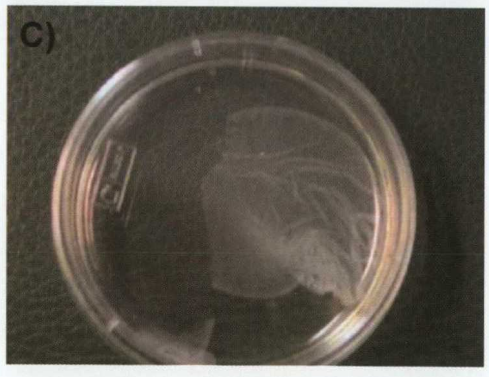
Regulatory T cells (Tregs) are another specific type of immune cells. They do not actively participate in the fight against infections, but their task is to suppress any excessive activation of other cells. The absence of those cells, or their serious dysfunction, causes severe, multi-organ damage of autoimmune etiology, and less severe quantitative disorders and dysfunctions of Tregs have been described in most autoimmune diseases and allergies. The activity of Tregs is extremely accurate as they mainly act through direct contact. Tregs and autoreactive target cells communicate with each other via membrane receptors. Therefore, this reaction is precisely targeted and limited to sites of inflammation. Consequently, potential side effects associated with other tissues that are characteristic of classical immunosuppressive therapy with non-cellular drugs are limited.

They were used for the first time to treat graft versus host disease after bone marrow transplantation, in which immune cells originating from the transplanted bone marrow attack the recipient's tissue. Our team at the Medical University of Gdansk has started administering Tregs to patients with this disease in whom standard therapy failed to yield positive results. They receive Tregs from the same donors from whom they had previously received their bone marrow transplant.

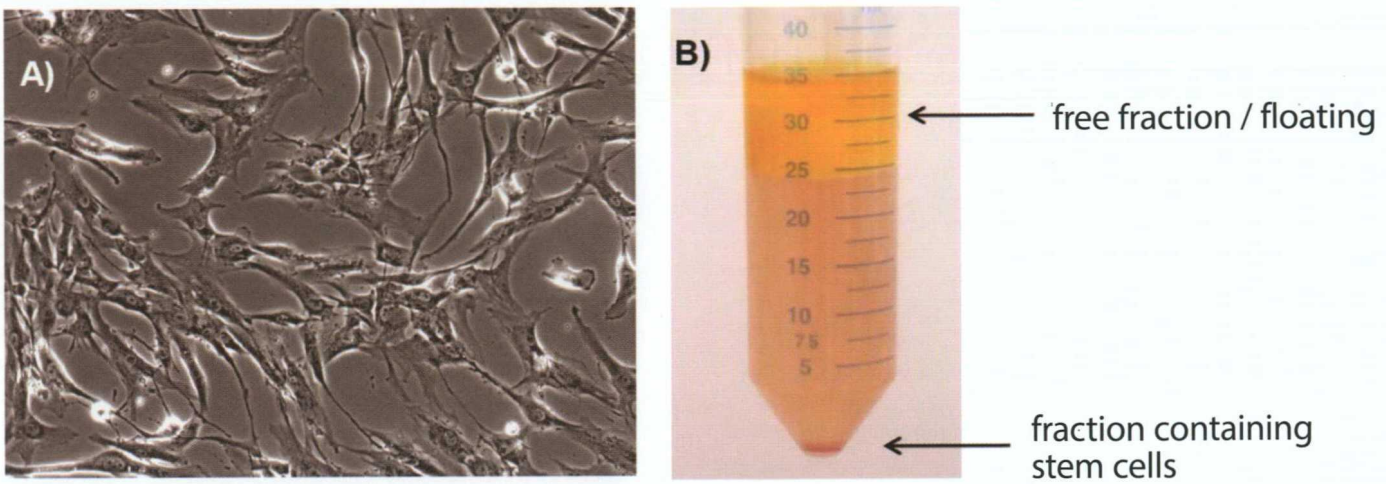
Our team also uses Tregs to treat type 1 diabetes, which is associated with the







Epidermis from adult stem cells produced at GUMed: A – epidermal stem cells immediately after extraction, B – epidermal stem cells differentiating into a mature tissue, C – gross image of the epidermis ready to be applied to a wound as a biological dressing



Mesenchymal (adult) stem cells produced at GUMed: A – stem cells in culture, B – gross image just after isolation from adipose tissue

destruction of pancreatic cells by the patient's immune system. Preliminary results show that this treatment does not cause any serious side effects, which is especially important in children, being the majority of patients with type 1 diabetes. From the clinical point of view, the advantage of this therapy is that patients treated with Tregs take less insulin than usual or can take no insulin at all.

Why so expensive?

Cells for clinical use must be prepared under specific conditions, in "cleanrooms" at pharmaceutical plants, which apply a strict hygiene regime akin to that used at integrated circuit factories. The air quality standard in such laboratories is described as "class 100" - which means that there must be fewer than 100 dust particles 0.5 micron in size (comparable to the smallest bacteria or smaller) per a cubic meter of air, with no larger particles present there at all. By comparison, the air in everyday office rooms contains from tens of millions to even billions of such particles. To obtain an adequate standard, clean air is delivered to the laboratory through a system of filters, and the staff must wear sterile dust-free clothes. They enter the laboratory through a system of locks that completely isolate it from external factors, and the equipment used inside is usually specially designed to be easily cleaned and sterilized and specially certified to ensure that nothing might jeopardize the therapeutic cells produced in the laboratory.

While the stringent requirements in terms of ensuring hygiene and failsafe equipment can be overcome, a certain "over-regulation" of the process of registering and producing cell-therapy "drugs" still remains problematic. Constantly shifting legal footing and the growing requirements being imposed, particularly in terms of documentation, have resulted in a significant increase in the cost of cell therapy in recent years. This certainly affects the availability of treatment for patients and, in the long term, can lead to a slowdown in research in this area, which in turn will affect the patients. This situation raises understandable opposition among physicians and patients, and although the regulatory institutions themselves can see the problem, no action has yet been taken to make it easier for research establishments to manufacture cell therapy drugs. As a result, the future of cell therapy is likely to be dependent on big pharmaceutical companies that have sufficient budgets for research in this field. But the question is, what will the cost to the patient be, and does it really need to be so high? ■

Further reading:

Trzonkowski P., Pikuła M., Marek-Trzonkowska N. (2013). *Cellular therapy in medicine.* Skrypt Międzyuczelniany Wydział Biotechnologii UG_GUMed.

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