

Promising dead ends for patients

Warning: Unproven Stem Cell Therapies

“Unproven stem cell therapies” are commercially available medical therapies that have not been tested for their safety and effectiveness in the context of clinical trials and have no official authorization or approval. However, depending on the nature of the cell preparation and the country in which the treatment is carried out, such authorization or approval is not necessarily required for the marketing of such products. In many cases, there is no detailed information provided about the cells used or their derivatives, the method of application, and the targeted effect. Nevertheless, several hundred clinics, doctor’s offices, and other facilities throughout the world offer stem cell based products and therapies for the treatment of often incurable diseases.

The providers of such therapies are typically based in China and Mexico; however, can also be found in the USA and Central Europe. Using a scientific logarithm, a study carried out in 2016 identified 417 independent, international websites offering stem cell therapies (Berger I. et al., 2016, Global Distribution of Businesses Marketing Stem Cell-Based Interventions, *Cell Stem Cell*, 19, 158-162). In addition to 187 providers in the USA, 11 were also recorded in Germany. Frequently changing websites without any detailed description of the treatment method used, supposed patient recommendations, and treatment locations in unnamed third countries make it difficult for the responsible authorities to legally classify these companies and trace them. Factors that all such providers have in common is that they extol the unique regeneration potential of stem cells and target individuals in often desperate situations.

Considerable medical demand

Stem cell researchers and scientific organizations often find themselves faced with requests from patients and their families for treatment options using stem cells. The spectrum of the diseases involved ranges from multiple sclerosis and Parkinson’s to amyotrophic lateral sclerosis (ALS) and diabetes mellitus. Patients also express interest in the treatment of “rare diseases” like sickle cell anemia and infantile brain damage, for example cerebral palsy, with stem cells. These requests usually arise in the context of tragic case histories characterized by a high level of despair on the part of the patients and their families. However, requests relating to “rejuvenation” and cosmetic therapies (for example, anti-wrinkle treatments) are also received.

Authorized stem cell therapies available only in a few cases

What all such requests have in common is that the people involved are seeking stem cell based regenerative therapies. In the majority of cases, stem cell researchers and scientific organizations respond to these requests with the information that, although intensive research is being carried out internationally on innovative therapies and early clinical studies are already being carried out, an authorized, standard therapy is not yet available. Exceptions to this include the treatment of serious illnesses like leukemia using blood stem cells (hematopoietic stem cells). Thanks to the expansion and transplantation of skin epidermis and limbal stem cells, applications involving stem cell based therapies are also available in specialized clinics to accident victims with extensive burns or damage to the corneas caused by accidents involving chemicals, for example.

Different stem cell types on offer

With unproven stem cell therapies, different types of stem cells and derivatives are administered in different ways:

- Therapies involving embryonic stem cells (ES cells) or induced pluripotent stem cells (iPS cells), and cells that have been differentiated from them, are only offered in a few cases; however, the scientifically proven development potential (pluripotency) of these stem cells is often referred to on the providers’ websites to make the possibilities associated with stem cells appear plausible.
- Forms of therapy using fetal cells obtained from aborted fetuses were and are still on offer. Due to their differentiation potential, the post-therapy effects of the application of these cells are particularly dangerous and can lead to the development of tumors.
- Most of the offered treatments involve the administration of adult stem cells. The cells are often taken from the patient’s own iliac crest, making the use of the cells autologous, namely taken from the patient’s own body. The stem cells involved are probably autologous, mesenchymal stem/stroma cells (MSC) and/or hematopoietic stem cells. Allogeneic treatments, using cells that have not been taken from the recipient and involving cell donation by a relative, for example, are also offered. Little information is provided about the preparation and characteristics of the stem cells or about any additives that

Photo: Charité & BH / Claudia Schaar

Cardiomyocytes derived from iPSCs stained for Troponin T (yellow) and Nuclei (blue)

may have been added to the cell transplant. Vague references are made here to “purification”, “concentration” and the “addition of further regeneration-promoting substances”.

The method and site of application can also pose sources of risk for patients. The cell transplant is often administered into the diseased organ or close to it. Descriptions of intercardial, intrathecal, and perineural administrations (injections into the heart, into fluid-filled space of the central nervous system, and into the tissue surrounding neurons) can also be found. In two incidents that took place in the Xcell-Center clinics based in Cologne and Dusseldorf until 2011, patients were seriously injured as a result of complications during intrathecal administration. Prices for such treatments are rarely quoted on the publicly accessible websites. It may be concluded from known cases that fees in the range of thousands to tens of thousands of euro (ca. 3,000 to 30,000 euros) are charged, depending on the provider and the administered therapy.

The difficulties facing the responsible supervisory authorities in taking action against the provision of such treatments, the therapeutic success of which is neither ensured nor likely, arise in part from the characteristics of the cell preparations intended for use. Special authorization is often not required at international level for therapies involving autologous stem cells or cell preparations that are used directly in the same treatment room and on the same date (“point of care”), and that are intended to carry out the same original biological functions in the body after the treatment (“homologous use”).

Typical patterns in the provision of unproven stem cell therapies

Stem cells are not always directly involved in regenerative processes in the body. For example, they can trigger so-called immunomodulatory effects at the site of the disease, for instance through the release of growth factors, and activate the body’s self-healing forces in this way. This effect is subject to current scientific debate and is also being tested in numerous clinical studies for a series of MSC applications. Factors secreted by MSCs, for example in extracellular vesicles, are also presented as a mechanism for observed positive effects. These scientifically proven arguments, which have been introduced into the field by researchers, also give the providers of unproven therapies a line of argument that is difficult to refute scientifically. Moreover, in the context of the treatments offered to patients, which are mostly described on publicly accessible web-based platforms, the link between the information about stem cells and their confirmed characteristics and the offered treatments is only made indirectly. Scientifically proven facts are correctly presented in one text and the proposed treatments are then described in separate texts on the same website. Patients are thus given the impression that the success of the treatment is scientifically proven without this being stated specifically by the provider. The impression is also usually given that the application of the proposed stem cell preparation can be used to treat a large number of different diseases. However, it is difficult to conceive scientifically of how one type of stem cell preparation is supposed to heal diseases as varied as autism, cystic fibrosis, and diabetes.

Max Planck Institute for Heart and Lung Research (MPI-HLR)

The Max Planck Institute for Heart and Lung Research, located in Bad Nauheim, investigates developmental processes of organs in the cardiovascular system and the lung.

A second focus is molecular and cellular processes during the formation of diseases in heart, blood vessels and lung, including remodeling processes in these organs. Scientists at the institute search for new approaches to support repair and regeneration of the affected organs.

The MPI closely cooperates with universities in Frankfurt, Gießen and Marburg. It has become a major part of various federal and state excellence initiatives and contributes to two “Gesundheitsforschungszentren”.

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Patients are also given the impression of high medical standards through the specification of the nationality of the senior clinician or the location of the clinic in a country with strict regulations (e.g. in Central Europe). The actual treatment, however, is often carried out in countries with less stringent standards. “Stem cell tourism” is now an acknowledged phenomenon.

Hope for patients?

What do unproven therapies mean for the affected patients? Testimonials by individual patients and surveys carried out among persons who have received such treatments are usually positive; however, it may be assumed that placebo effects are also frequently at work here. Individuals who are hoping for a cure and have spent a large sum of money on it along with additional travel and accommodation costs, will often initially assess the treatment as positive and also feel better on a subjective level.

Still, in some cases, an unproven therapy can have painful and exacerbating consequences, which may even result in fatalities. Official data has not been published on this gray area, yet such conclusions can be drawn from the few published results available. The XCell-Center clinic in Cologne and Dusseldorf was closed down when a two-year-old boy from Italy died following complications after the injection of stem cell preparations into his brain. Unproven therapies have also had serious consequences for the affected patients in recent times. For example, the treatment of macular degeneration with stem cells in a clinic in Florida resulted in permanent blindness in three patients.

Legal classification of unproven stem cell therapies

Legally, the general requirements for therapies that have not undergone any clinical studies are applicable to stem cell therapies. In Germany and the entire European Union, therapies based on autologous adult stem cells must generally be classified as advanced therapy medicinal products (ATMP) and are thus subject to Regulation (EC) No 1394/2007 (ATMP Regulation). In the scheme of this regulation, the majority of such products involve somatic cell therapies. Following a transitional phase up to the end of 2012, since 2013 all ATMPs have been subject to a central authorization process, which is coordinated by the European Medicines Agency (EMA) and requires clinical testing among other things.

Hard cases prompting “compassionate use” are excluded from the requirement of central authorization (§ 21, sub-section 2, no. 6 of the German Medicinal Products Act, AMG). This is intended to cover the provision of authorized drugs (including ATMPs) free of charge to seriously ill individuals. The second exemption, known as the ‘hospital exemption’ (Art. 28, section 2 of the ATMP Regulation, implemented under German law as § 4b AMG). According to this provision, ATMPs may be administered to individuals without central authorization or approval if the therapy: 1) is prescribed by a doctor as an individual preparation for a single patient; 2) is not routinely produced in accordance with specific quality standards; and 3) is used in a specialized medical facility under the expert responsibility of a doctor (§ 4b, sub-section 1, no. 1 AMG).

The legal regulations on the permission-free production of drugs by doctors as well as in particular the freedom of medical treatment (i.e. clinical application) by the physician with production and use under personal responsibility often open up the gray area for unproven therapies. The providers of autologous stem cell therapies in Germany are subject to a particular regulatory framework. Thus, from a regulatory perspective, the options available to users of unproven stem cell therapies are relatively limited in Germany.

However, the scope available to providers, even in other EU Member States, is very different – and even more so in the case of those located outside the EU.

Counteraction through credible and effective communication

In summary, it may be confirmed that, in view of the large number of legal issues involved and the highly heterogeneous regulatory situation, it is very difficult to control the phenomenon of stem cell tourism and the availability of unproven stem cell therapies. Instead, in the years to come, it will be a question of providing comprehensive and transparent communication about the scientifically proven therapies that may be expected, and to distinguish them

clearly from “unproven therapies”. The aim must also

be to provide patients and their relatives with material that enables them to evaluate proposed therapies in relation to the professionalism of the providers and the likelihood of success of the proposed therapeutic approach. National and international professional associations have a key responsibility here. However, it must be admitted that, in reality, the scope of such a communicative approach is very limited. First, the media profile of professional medical associations and their positions is often limited and restricted to professional circles. In many cases, even family physicians, who, as primary care providers, are often the first point of contact for patients considering stem cell therapy, are inadequately informed about current therapeutic options with stem cells and the recommendations of the professional associations. Thus, in the interests of patient protection, a very good and continuous exchange of infor-



Heidelberg Institute for Stem Cell Technology and Experimental Medicine (HI-STEM)

HI-STEM gGmbH is a non-profit public-private partnership between the German Cancer Research Center (DKFZ) and the Dietmar Hopp Foundation (DHS).

Located within the DKFZ in Heidelberg, HI-STEM performs cutting-edge research on stem cells with the aim of translating these results into novel clinical applications. This includes the development of novel diagnostic tools and innovative therapies to monitor and target leukemic and solid tumor stem cells as well as metastatic disease. Professor Dr. Andreas Trumpp and five Junior

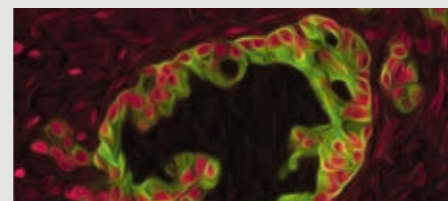
Group Leaders direct an international research team of more than fifty employees.

The HI-STEM Research Groups:

- Hematopoietic and Leukemic Stem Cells (A. Trumpp)
- Stem cells at the interface of hematopoiesis, immunity and cancer (S. Haas & A. Trumpp)
- Experimental Hematology (M. Milsom)
- Stress induced activation of HSCs (M. Essers)
- Cancer Stem Cells and Metastasis (M. Sprick & A. Trumpp)
- Metastatic Niches (T. Oskarsson)



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mation between patient associations, professional associations, and general practice is a matter of absolute priority.

Yet, even the best communication and information will not be able to prevent providers of unproven stem cell therapies from continuing to make healthy profits on the back of patients' hopes. The number of clinics offering stem-cell-based therapies for different indications has continued to increase in recent years. In Australia alone, where the phenomenon of stem cell tourism has been researched in detail, between 2011 and 2014, over 40 clinics included unproven stem cell therapies in their range of services or offer such therapies exclusively.

What is important is that the scientific community accepts that especially patients to whom conventional medicine offers few or no alternatives will be increasingly willing to

try out “alternative” methods using their own resources and that, thanks to the Internet, they will also be able to access such services quickly. This can only be counteracted through the careful communication of research results and the dissemination of information that enables patients to make well-informed decisions.

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This article is an excerpt from the book published by the Berlin-Brandenburg Academy of Sciences and Humanities (BBAW): “Stammzellforschung. Aktuelle wissenschaftliche und gesellschaftliche Entwicklungen”, chapter 6. “Ungeprüfte Stammzellangebote”.

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