SPOTTING 'UNPROVEN' STEM CELL THERAPIES IN THE WILD

Freya Leask explores how to spot an 'unproven' stem cell-based therapy and why producing an effective stem cell-based therapy is so challenging.

When Masayo Takahashi (Figure 1) shared the results of the first clinical trial testing induced pluripotent stem cells (iPSCs) in humans in the *New England Journal of Medicine*, she was surprised to see, next to her article, another article reporting on the same autologous stem cell-derived treatment.

Takahashi, formerly based at RIKEN (Japan) but who recently spun out a standalone company called Vision Care, made headlines in 2014 when she implanted a sheet of retinal pigment epithelium (RPE) cells, produced by first reprogramming the patient's own cells into iPSCs then differentiating them into the RPE cells, into the patient's eye to treat age-related macular degeneration. The process, which Takahashi described as *"a momentous first step"* towards applying iPSCs to regenerative medicine, was noteworthy for the its complexity and difficulty, as well as the speed at which it was carried out after the Japanese health ministry gave approval for a potential clinical trial.

By 2017, having followed the patient for a year to determine there were no ill effects, she was ready to publish her report. However, the other article, published by a coalition of physicians, had different news to share.

In the paper, the team describe three Florida patients who also received 'stem cell' treatments. However, unlike Takahashi's patient, they were left blinded after their treatment caused vision loss, detached retinas and hemorrhage. They had received an unproven treatment, seemingly without the careful planning and preparation that usually accompanies a procedure like this.

The term 'unproven treatment' is hugely emotive to scientists aiming to develop 'proven' treatments, commercial providers arguing against it, and patients looking for answers and, ultimately, hope. In 2015, the International Society for Cell Therapy (ISCT), now the International Society for Cell and Gene Therapy, set out to define exactly what makes a therapy 'unproven'.

HOW IT WORKS... OR DOESN'T

The first criterion to denote an 'unproven therapy' is the lack of scientific rationale to suggest potential efficacy. There's *"little evidence that adipose, bone marrow and amniotic stem cells can be used safely and effectively for the diverse array of conditions marketed by for-profit clinics,"* according to Paul Knoepfler, speaking to RegMedNet in 2018 [1]. Paul is a professor at University of California, Davis (CA, USA) and runs the noted stem cell blog *The Niche* [2]. He has been monitoring the rise of unproven stem cell treatments on *The Niche* as well as in peer-reviewed literature.

Although some studies have demonstrated that stem cell-based treatments can be safe, there is little clinical evidence of a high enough quality that indicates they are effective in humans [3].

There should also be an understanding of the mechanism of action to support clinical use of the therapy. In 2019, research conducted at Arizona State University (AZ, USA) into the clinics offering stem cell-based therapies found that although 60% of staff listed on the clinics' websites had medical degrees, over a quarter had other medical qualifications such as Doctor of Osteopathy, and Doctor of Chiropractic and Doctor of Naturopathic Medicine [4], a range of qualifications and specialties unlikely to have the expert knowledge into how and why stem cell treatments work the way they do, if at all.

A WOBBLY EVIDENCE BASE

Another reason to be wary of 'unproven' treatments is they may possess insufficient data from *in vitro* assays, animal models and clinical studies regarding the safety profile to support the use in patients. They may also misrepresent early-stage data showing safety as conclusive proof of efficacy.

Many businesses marketing unproven treatments make *"positive but imprecise, unquantified claims about the therapeutic promise"* ▶

Figure 1. Masayo Takahashi (right) was the lead scientist in the first human trial involving iPSCs. Kyodo News via Getty Images.

► of the stem cell interventions they promote,” explained Leigh Turner, Associate Professor at University of Minnesota Center for Bioethics, School of Public Health and College of Pharmacy (MN, USA), speaking to RegMedNet following his 2018 research into the Canadian landscape of unproven treatments. In the paper, he detailed the ways in which some clinics get around the lack of published evidence in the field.

“I’m very concerned about the risks associated with businesses making dramatic claims about stem cell treatments ... without doing the careful, costly and time-consuming work needed to develop a compelling evidence base for such representations,” continued Turner.

Such clinics are using “tokens of scientific legitimacy”, he explained, such as personal testimonials, eminent scientific advisory boards, professional affiliations and technical language to make their proffered treatment more acceptable [5]. Without links to “peer-reviewed publications, unpublished data or other sources of evidence”, it’s “impossible to know whether meaningful data support such assertions.”

The one thing patients need to remember, says Kieran Breen, Head of Research and Development, St Andrew’s Healthcare (UK): “If it sounds too good to be true, it probably is.”

QUALITY NOT QUANTITY

Living medicinal products, such as stem cell-based treatments, are complex by nature and generally involve multiple steps to produce a quality product. ‘Unproven’ products, according to the ISCT, lack a standardized approach to confirm product quality and ensure consistency in cell manufacturing, or are used within nonstandardized or nonvalidated administration methods.

With the many stem cell-based therapies currently under investigation, a sample of patient or donor cells is collected and is then expanded. Cell lines can also be obtained from validated cell banks. In her first trial, Takahashi used autologous cells, or cells obtained

from the patient receiving the therapy. In the second, she obtained cell lines from the CiRA iPSC bank (Japan) [6].

The cells are then differentiated, with multiple quality controls at every step. These measures range from assessing the cells’ morphology, viability and density to potential tumorigenicity and presence of viral or mycoplasma contamination, as well as looking for specific cell surface markers to ensure the desired final cell type has been produced [7].

With Takahashi’s first trial, after this stage an RPE cell sheet was surgically implanted into the subretinal space of the patient’s eye. The process took 10 months, from initial skin biopsy to collection of patient fibroblasts to production of an RPE cell sheet that was ready to be implanted. Since then, other cell-based treatments have reported manufacture times of around 3–4 weeks [8].

By contrast, the Florida patients received a therapy much closer in nature to their original cell sample. A sample of adipose tissue was obtained via liposuction and stromal vascular cells were separated out using enzyme treatment and centrifugation. This cell fraction was then resuspended in a small amount of platelet-rich plasma, separately obtained from a sample of the patient’s whole blood, before being used immediately for intravitreal injection [9].

There are usually many more steps in producing a cell or gene therapy, explains Karen Magers, Head of Regulatory for Cell & Gene Technologies, Lonza Pharma & Biotech (Switzerland), because “the manufacturing process is designed with the objective of consistently manufacturing products derived from cell-based starting material that meet target quality attributes linked to the desired patient safety and clinical outcome.” Ultimately, a standard, effective product is vital before it can be administered to human subjects.

Why is there such a difference between the treatments? The answer lies in a definition that has been rigorously debated since its inclusion in a publication of 2005.

MINIMAL MANIPULATION... OR NOT

The FDA is responsible for regulating an exhaustive list of products to ensure the safety of the US public, including therapeutic products such as cell therapies. Most of the products require a new drug application or biologics license application before they can be marketed. The process of securing a new drug application or biologics license application can be lengthy, as rigorous preclinical and clinical study data are required. Could there be a way of bringing the benefits of stem cell-based therapies to patients without have to submit so much paperwork?

Many clinics currently marketing ‘stem cell-based’ treatments, of which there may be over 700 in the US alone [10], cite an exemption over ‘minimal manipulation’ and ‘homologous use’. Where a human tissue or cell-based product has been minimally manipulated – for example, nothing more than centrifugation or cryopreservation – and will produce the same function in the recipient as they did in the donor, it doesn’t need the formal approval of the FDA.

“The unproven clinic part always muddies the waters and risks damaging the public’s perceptions of stem cell research and regenerative medicine.”

However, Magers explains, “As manufacturing steps completed to produce cell-based products have the potential, and in many cases the intended outcome, of altering the relevant characteristics of the cells, the processing that occurs during the manufacturing process is more than minimal manipulation.” As an example, “if cells are isolated from structural tissues such as adipose tissue, the process of isolating the cells is more than minimal manipulation ... manufacturing steps that alter biological characteristics such as metabolic activity, differentiation state or proliferation potential [are] more than minimal manipulation.”

The FDA agrees, and since 2017 has taken a tougher line on ‘unproven’ clinics, sending out warning letters and even taking some to court [11].

WHERE THERE'S A WILL, THERE'S A WAY

The problem with the ‘unproven clinics’, explains Takahashi, is that the patient desire is there. “Patients come from all over Japan” to her clinic in Kobe; “we’re not treating anything”, she says, “but still they come”. For some patients, the risk of the unknown is worth the risk.

“My vision was very poor ... I was unable to read, see faces, or drive,” says Doug Oliver, who received a stem cell transplant to treat his macular degeneration and now advocates for patients in the regenerative medicine field through founding the Regenerative Outcomes Foundation. “I was suicidal just 2 years prior” to his treatment, he explained. Five months later, he got his driving licence back.

However, the information he received was “simple and general”. In the case of the Florida patients, at least two out of the three believed they were taking part in clinical trials, and inability to provide proper informed consent due to inadequate information is yet another ISCT hallmark of an ‘unproven’ treatment.

Before his 2018 work into the Canadian stem cell landscape, in 2017, Turner investigated businesses using ClinicalTrials.gov, a registry of clinical trials run by the United States National Library of Medicine and currently holding registrations from over 318,000 trials from 209 countries in the world. He was alarmed to see companies using this registry as an exercise in ‘direct-to-consumer’ marketing.

“If you take a careful look at many of these pay-to-participate studies you find what in numerous cases appear to be studies with serious scientific and ethical shortcomings ... in some instances, there is no record of peer-reviewed preclinical studies being done before stem cells are administered – for thousands or tens of thousands of dollars – to humans,” Turner explained. Without businesses being transparent about the evidence that exists for these treatments, “patients are exposed to an unnecessary and avoidable level of risk when they pay to participate in such studies.” [12].

PUBLIC PERCEPTION & FUTURE DEVELOPMENT

“The unproven clinic part always muddies the waters and risks damaging the public’s perceptions of stem cell research and regenerative medicine,” explains Knoepfler, who often deals with emails from desperate patients looking for information [1].

Oliver believes that more patient education is needed: “as regulatory expectations become clearer and take more form in the US, it is clear the real ‘bad actors’ are getting worse.” The process of manufacturing and receiving a stem cell-based treatment needs to

Figure 2. In his original *Regenerative Medicine* article, Knoepfler mapped the complex and interwoven stem cell ecosystem. The degree of separation, or lack thereof, means that unravelling the relationships between stakeholders is time-consuming, and identifying where education and authority would be of most benefit is difficult [13].

be made more transparent, to “standardize informed consent, provide opportunity for patient input, and train practitioners to gather robust data that can actually be used in clinical trials.”

If the real bad actors aren’t dealt with soon, he says, more “patients will start getting hurt”.

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