Exploring stem cell therapies: an interview with Darius Widera

Article

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Darius Widera is a Professor of Stem Cell Biology and Regenerative Medicine at the University of Reading (UK). His career in stem cell research began in the industry, where he was involved in method development utilising haematopoietic stem cells at Miltenyi Biotech (Germany). He earned both his Master's degree in Biochemistry and PhD in Neurobiochemistry from Witten/Herdecke University (Germany). During this time, his work focused on neural stem cells, neural crest-derived stem cells, and development of novel clinically compliant 3D cell culture methods. In 2012, Darius served as a Principal Investigator at the University of Bielefeld (Germany), before relocating his lab to the University of Reading in 2015.

Your lab focuses on harnessing the potential of mesenchymal stromal cells (MSCs) and neural crest-derived stem cells. Could you tell us more about these stem cell types?

Neural crest-derived stem cells (NCSCs) are a fascinating type of adult stem cell. Most adult stem cells are merely multipotent, meaning they can differentiate solely into cell types specific to their tissue of origin. For example, blood-derived stem cells can only differentiate into blood cells. Similarly, neural stem cells from the brain can only differentiate into neural derivatives, such as neurons or astrocytes, and lack the ability to generate blood cells.

In contrast, NCSCs are closely related to early developmental stages, allowing them to differentiate into both ectodermal and mesodermal cell types (PMID: 22170630). As a result, they have the potential to differentiate into cells such as bone, cartilage, adipose tissue, and peripheral nerves. With appropriate protocols, they can also be reprogrammed into central nervous system neural stem cells (PMID: 25331182). Subsequently, they can be differentiated into neurons, such as dopaminergic neurons, that could potentially be used to treat Parkinson's disease (PMID: 25479965). This high differentiation potential and the relative abundance of the source material make NCSCs promising candidates for clinical translation.

In contrast to NCSCs, the differentiation potential of mesenchymal stem cells (MSCs) is considerably lower, and even their stemness is quite controversial. Originally described by Friedenstein as bone marrow-resident cells with fibroblast-like morphology in culture (Friedenstein A, Petrakova KV, Kurolesova A, Frolova GP. (1968) Heterotopic of bone marrow. Analysis of precursor cells for osteogenic and hematopoietic tissues, Transplantation. 6, 230-47. Friedenstein AJ, Chailakhjan RK, Lalykina KS. (1970) The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells, Cell and Tissue Kinetics. 3, 393-403), MSCs have been initially referred to as mesenchymal stem cells. Later on, the definition of MSCs also included the expression of a defined marker panel and the ability to differentiate into bone, cartilage, and adipose cells.

Promising pre-clinical research and several clinical trials suggested that MSCs can alleviate symptoms of multiple conditions with inflammatory components. However, more recent studies revealed that transplanted MSCs do not integrate and differentiate into the lost cell types but exert their effects via the reduction of inflammation and modulation of the immune system toward a more anti-inflammatory state. This view is now widely accepted, and Arnold Caplan, who initially coined the term mesenchymal stem cells, recently suggested referring to MSCs as 'medicinal signalling cells'.

Interestingly, there is little difference between MSCs and fibroblasts. If we isolate fibroblasts, their expression of MSC markers is identical to that of MSCs. Also, under appropriate conditions, fibroblasts can differentiate into bone, fat, and cartilage cells. Moreover, we have observed that the paracrine effects attributed to MSCs can be observed when fibroblasts are used. Considering all of this, I personally believe that they are the same. Nevertheless, the paracrine regenerative effects of MSCs are pronounced, and thus, the clinical potential of MSCs remains promising. However, considering their mode of action, transplantation of MSCs can likely be substituted by harnessing their secretomes.

What are some of the key considerations for commercialization of MSC-based therapies?

When we look at the commercialisation of stem cell-based therapies, it's important to consider regulatory issues at an early stage. The regulatory framework related to cell transplantation is well defined within the European market, in the USA, and in the UK. However, when we look at mesenchymal stem cell-derived biologics such as extracellular vesicles, the regulatory landscape differs. In Europe, there are already attempts to regulate this, and in the US, this area is already tightly regulated. However, in the UK, we still have no definitive regulation around the use of these biologics. When we consider commercialisation, regulations need to be taken into consideration.

Additionally, when looking at commercialisation, you need to consider how to design the project at an early stage since one of the major bottlenecks is upscaling. It's one thing to expand and differentiate the cells on a small scale or to isolate extracellular vesicles for pre-clinical research, but if it comes to clinically relevant quantities, many processes are challenging to translate. different. This can be addressed by different technologies such as flask stacks, 3D cell culture, bioreactors, or combinations of these techniques. If implemented at early stages, all of these techniques can save money and time.

Given your focus on mesenchymal stem cells, do you believe this approach holds more promise compared to using induced pluripotent stem cells?

As I mentioned before, even if we consider MSCs to be true stem cells at all, they are merely classified as multipotent stem cells. We know that they can only differentiate into certain derivatives of the mesodermal lineage, including bone tissue, adipose tissue, and cartilage. However, these cells are not able to differentiate into cells such as neurons. That being said, MSCs are already a clinical reality and have been used in multiple clinical trials targeting not only conditions of the mesoderm but also conditions targeting ectodermal tissues such as the brain.

The first data sets from some of these clinical trials are encouraging. Nowadays, the general consensus is that the mode of action of MSCs is paracrine. Briefly, this means that MSCs release factors that regulate inflammation and modulate the immune system, thereby promoting tissue regeneration and the re-establishment of tissue homeostasis.

In contrast, if you use pluripotent stem cells, such as induced pluripotent stem cells (iPSCs) or embryonic stem cells (ESCs), you can, in fact, replace nearly every single cell type in the body. However, the application of induced pluripotent stem cells in the clinic has certain risks. As the cells can differentiate into so many cell types, you need to pre-differentiate them before you transplant them. Otherwise, there is a risk of ending up with unwanted tissue or even tumours.

In addition, over the last decade, it has been demonstrated that reprogramming cells can result in mutations resembling those found in cancer cells. Therefore, if you are considering translating this type of therapy into a clinical setting, you have to be very careful. I would advise sequencing every iPSC line that you plan on using in a clinical context.

What do you consider to be some of the limitations of mesenchymal stem cells (MSCs).

Considering the limitations, it's important to remember that MSCs are adult somatic cells and thus will be affected by cellular ageing. After around 10 to 12 passages, you will notice the first signs of cellular senescence as the telomeres shorten with each cell division. Therefore, the time available to obtain clinically meaningful cell numbers is very limited, and you are likely to have batch-to-batch variability. This limitation, coupled with the fact that MSCs are unlikely to integrate, might also mean that patients could require repeated injections. This could be addressed by immortalisation of the cells. However, by immortalising them, we face similar risks to those seen during the reprogramming of cells, such as the development of cells with tumorigenic characteristics.

Last year, you published a paper on unregulated stem cell-derived products and the rise in the number of direct-to-consumer businesses offering these products. What needs to be done by regulatory boards to ensure greater transparency from businesses concerning the regulatory status of these products?

In this study, we mapped the landscape of unlicensed direct-to-consumer businesses offering interventions based on stem cell secretomes, exosomes, and extracellular vesicles. In many cases, we observed that these unregulated businesses are offering secretomes isolated from MSCs or other undisclosed stem cell sources. Importantly, to date, there are no approved and licensed therapies and interventions based on MSC secretomes.

In the US, the FDA has already tightened regulations around this. However, with the rise in the number of unregulated businesses, regulatory bodies often lack the capacity to enforce their policies effectively, resulting in significant challenges.

When it comes to any medical intervention, we need to consider not only efficacy but also safety. Important factors include quality control, sterility, and the absence of endotoxins. The entire process must be closely regulated, yet in many instances, we found no evidence of rigorous control measures implemented by these businesses. What's even more concerning is that these businesses offer interventions for conditions where the suggested therapy lacks any scientific backing. Costs are another important factor to consider. For example, businesses are offering secretome interventions for the treatment of autism, with each injection costing up to $25,000. Often, these businesses sell multiple rounds of injections, significantly increasing the overall costs and risks. I think it's important for us as scientists in the field to raise awareness about these interventions and their associated risks.

What measures can be taken to educate the public about the risk of unproven stem cell interventions and reduce misinformation, therefore, minimising harm?

We need to engage more with the general public. I believe it should be a priority to protect them through education. As scientists, we should also interact more with regulatory bodies, advocating for tighter control around these interventions. Lastly, working with the media is

essential. Recently, there has been a surge in mainstream media interest calling for tighter regulations, which is crucial for raising awareness.