

## EQUINE STEM CELL THERAPY IN REGENERATIVE MEDICINE – WHERE ARE WE NOW AND WHERE ARE WE GOING?



In the past decade, the number of studies published in the field of stem cells and regenerative medicine has increased exponentially, and the popularity of this research area does not seem to slow down. So with all this new knowledge, why is it that we still only have a limited number of established stem cell based therapies?

Why have most of the therapies failed to live up to our – admittedly very high – expectations? Where are we right now? And what is the future for stem cell based regenerative medicine?

When stem cells\* were first introduced as a cell source for regenerative medicine, the belief was that they could radically change the way we treat a wide range of diseases both in humans and in veterinary practice. Basic studies on the characteristics and properties of these cells had revealed impressive abilities, and the promises made by researchers and companies were endless.

On the positive side, stem cells are still impressive and exciting and may have even more abilities than we first expected, and their potential in regenerative medicine is huge. However, a number of factors may have contributed to the so far limited success of stem cell based regenerative medicine.

In this brief abstract the following issues will be addressed, but several others are also relevant:

1. Are the cells used really stem cells?
2. What is the role of the stem cell in the regenerative process?
3. Case selection
4. Evidence based therapy – case reports versus original research

### 1. Is the cell a stem cell?

Another presentation at this years meeting will discuss stem cells in more detail, and there are a number of very good reviews available. But in order for a treatment to be a stem cell based treatment, we have to be sure that the cells used have stem cell like properties. Adult stem cells (MSCs) are a very small subpopulation of cells no matter whether the tissue source is bone marrow, adipose tissue, cord blood or others. In order for a cell-based therapy to be a stem cell therapy this subpopulation has to be isolated from the tissue-specific cells. There have been a number of attempts to identify cellular markers unique to MSCs, but so far the results have been insufficient, especially in the horse. Currently, our only established method to isolate MSCs is to utilise their adherence to plastic surfaces. This is a rather crude selection step. Further steps to validate for stem cell like properties are rarely if ever performed outside of research projects.

In addition, the stem cell number in the initial sample will be very low, so an expansion step may be necessary to achieve desired cell numbers. This takes time and money even though procedures have been improved, so if a commercial product promises to return **stem cells** ready for therapy in a few days, please be sceptical. The product may have an effect (see #2), but it is not what would normally be characterized as stem cell treatment.

### 2. Does it have to be a stem cell?

The next question is: do we need a pure MSC population in order to achieve regeneration and improvement? The traditional approach of implanting cells and expecting them to replace damaged tissue with new tissue may turn out to be too simplistic. Recent studies suggest that the actions of MSCs may be far more subtle and indirect than straightforward tissue replacement. MSCs may elicit trophic effects, regulate pain, or even be immuno-modulatory. If this is true, a limited number of cells may be sufficient to achieve the desired effect, and the pureness of the cell preparation may be less important. This is a very exciting perspective that requires more research.



### 3. Case selection

This point is universal for novel therapies. Cell based therapies, especially those involving isolation and expansion of an autologous MSC subpopulation, are expensive, time-consuming and not off-the-shelf. For these reasons, cases selected for this treatment in a general equine practice will not be the uncomplicated cases, but are much more likely to be cases that have already undergone a number of other treatments without success. With time the damage will have progressed and/or reached a more chronic stage, and secondary problems may have developed; making these cases very difficult to treat even for a product with regenerative potential. In addition, companies tend to promote new treatments to an extent where the equine practitioner can only be disappointed or disillusioned, because the product almost invariably will not be able to perform to the magical standards promised.

### 4. Evidence based treatments versus case reports

The market of stem cell treatments for regenerative medicine is flooded with case reports and miracles making it very hard for veterinarians and clients to separate the good from the bad. The lack of properly controlled studies in our field is disturbing - we need more controlled studies! Admittedly, controlled studies on naturally occurring disease in large animals like the horse are both difficult and very expensive to perform. But as long as we accept that the different treatment options have not been tested and validated, the market will remain murky and open to less-than-serious operators. This hurts all the serious and diligent providers of cell based therapies. It is promising that a few relevant and thorough studies have been presented recently, but there is still a lot of work to do.

In conclusion, the take home message is that stem cells in regenerative medicine remain very exciting and promising even though the road to success has turned out to be a lot more complicated than first expected.

*\* Please note that there is a lot of controversy regarding the nomenclature of cells with stem cell like properties. For the purpose of simplicity, in this text the term stem cell refers to any cell with stem cell like properties. This includes (mesenchymal) stem cells, mesenchymal progenitor cells, and mesenchymal somatic cells.*