MESENCHYMAL STEM CELLS HEAL DIFFERENTLY, RESEARCH SHOWS

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### ****The Mesenchymal Stem Cell Journey Experienced by a Researcher****

My four-year old daughter recently learned the infamous question, “Are we there yet?” As we approach almost 30 years after the discovery of mesenchymal stem cells (MSCs), it seems that effective MSC therapies should be within grasp.

**So the question of importance becomes, after three decades of research into the properties of MSCs, why aren’t we there yet?**

For a decade or so, MSCs were unfairly overlooked and largely thought of as a supportive, feeder layer for hematopoietic stem cells.

Then, the pendulum swung strongly in the opposite direction, with MSCs prematurely labeled as “stem cells,” based on a substantially limited differentiation potential. This misleading term, drove research towards outcomes that involved semi-differentiated and often non-engrafting cells.

In my opinion as a MSC researcher, one of the main reasons that the cell type has not reached its potential is that MSC differentiation, along with its straightforward mechanism of action, often does not explain the benefits of MSC treatment. The answer to how MSCs exert their effects is still questioned.

The traditional view that mesenchymal stem cells heal by maturing into replacement cells for damaged tissue is either partially (or fully) untrue. The real authority of these cells comes from their ability to regulate the immune response and spark the body’s own regenerative machinery, research into the cell type now shows.

Although scientists and the regulatory bodies, such as the FDA, often struggle with this lack of specificity, it has generated hundreds of clinical trials that are now investigating how MSCs can be used to treat a variety of diseases (around 450 trials at clinicaltrials.gov).

### ****Future Directions for Mesenchymal Stem Cell (MSC) Research****

**In my experience as a MSC researcher, I believe future research should consider:**

1. **Is MSC treatment better than using the whole mononuclear cell population (MNC)?**MSCs originate from MNCs (MSC only make 0.1-0.01% of those cells), which can be minimally manipulated and readily infused back into the patient. Few comparative analyses have shown MSCs are better for ischemic limbs in patients, and the addition of MSCs to a MNC injection improves the outcome of diseases. That means that an autologous MNC treatment, followed by MSC expansion from left over MNCs, becomes an attractive feature for more chronic diseases or diseases followed by some type of disability. (Note: Our department always has leftover MNCs from patients in a current phase 2 clinical trial.)
2. **What are the effects of scale up technologies on MSCs?**

Existing research has identified that cell confluence and the number of population doublings can impact a prominent therapeutic mechanism: the immunomodulatory potential of MSC. The degree to which this exerts its effects is still largely unknown and needs to be further explored. Personally, I believe that MSCs work better with fewer doublings.

1. **To what degree does donor variability impact outcomes?**

MSC scientists have long been aware that there is donor-to-donor variability. However, a recent study by Darwin Prockop, a pioneer in the MSC field, identified that it is preferable to seek female donors (as well as short donors, for that matter) to treat inflammation. The reason to seek female donors is that there is gender-specific expression of TSG-6, an anti-inflammatory protein. Therefore, looking for other markers similar to TSG-6, could provide valuable predictive information.

1. **Can we develop functional assays to look beyond classical MSC markers and differentiation capacity?**

It would be preferable to identify functional assays that can be performed in vitro, such as immune cell activation. For instance, if I am treating a patient with multiple sclerosis, I should seek out MSCs from the patient that can modulate his or her immune system. If the patient’s MSCs do the job well, that is the optimal outcome. If not, we can next seek donors that are historically efficient at immune modulation. As a research group, we have repeatedly witnessed that some MSC donors are better than others at “promoting” or “driving” specific cellular outcomes. Obviously, this approach requires large bio-banks to store donor lines. It also means that if an effective donor is identified for a specific purpose, it should be marked appropriately and saved for future use. Functional assays will also help to assess MSC potency after any scale-up protocol.

1. **Can we find ways to “jump start” the therapeutic mechanism of MSCs even before infusion?**

MSCs are short-lived following infusion, but interestingly, the cells seem to be capable of sensing the biological action that needs to occur. For instance, if you have an inflammatory condition, MSCs will act as anti-inflammatory cells. If you require regeneration, MSCs will secrete growth factors. If you need your neural stem cells from the subgranular zone of the dentate gyrus in the hippocampus to differentiate into mature neurons, MSCs can promote this. Some researchers have even claimed that MSCs can help patients rid themselves of specific bacteria. This could occur by mimicking specific disease micro-environments, or possibly by using the patient’s own clues to trigger the desired therapeutic mechanism in MSCs.

1. **Is the use of MSCs in cancer patients to be avoided?**

Because cancer is essentially a continuously-growing wound, cancerous conditions can “trick” MSCs into attempting to resolve it and can accidentally support the growth of some (although not all) cancers. On the other hand, there are studies showing that specific conditioning protocols can turn MSCs into cancer-killing cells for specific, limited types of cancers. Therefore, as a research community, we need to acquire a greater understanding of how MSCs act within specific cancerous conditions and how they behave within individual patients.

### Directions for Future Mesenchymal Stem Cell (MSC) Research

By combining the research advancements discussed above with the discovery of new mechanisms of action, MSC efficacy and predictability will improve. Furthermore, the number of MSCs needed for therapy will decrease – a major hurdle to the use of MSCs for autologous treatments.  Finally, the use of MSCs for personalized medicine applications is on the verge of reaching clinical utility.

In summary, after three decades of preliminary research into MSCs, the next decade of MSC research will likely be the most exciting and innovative to date.