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Under the microscope: Mesenchymal Stromal Cells

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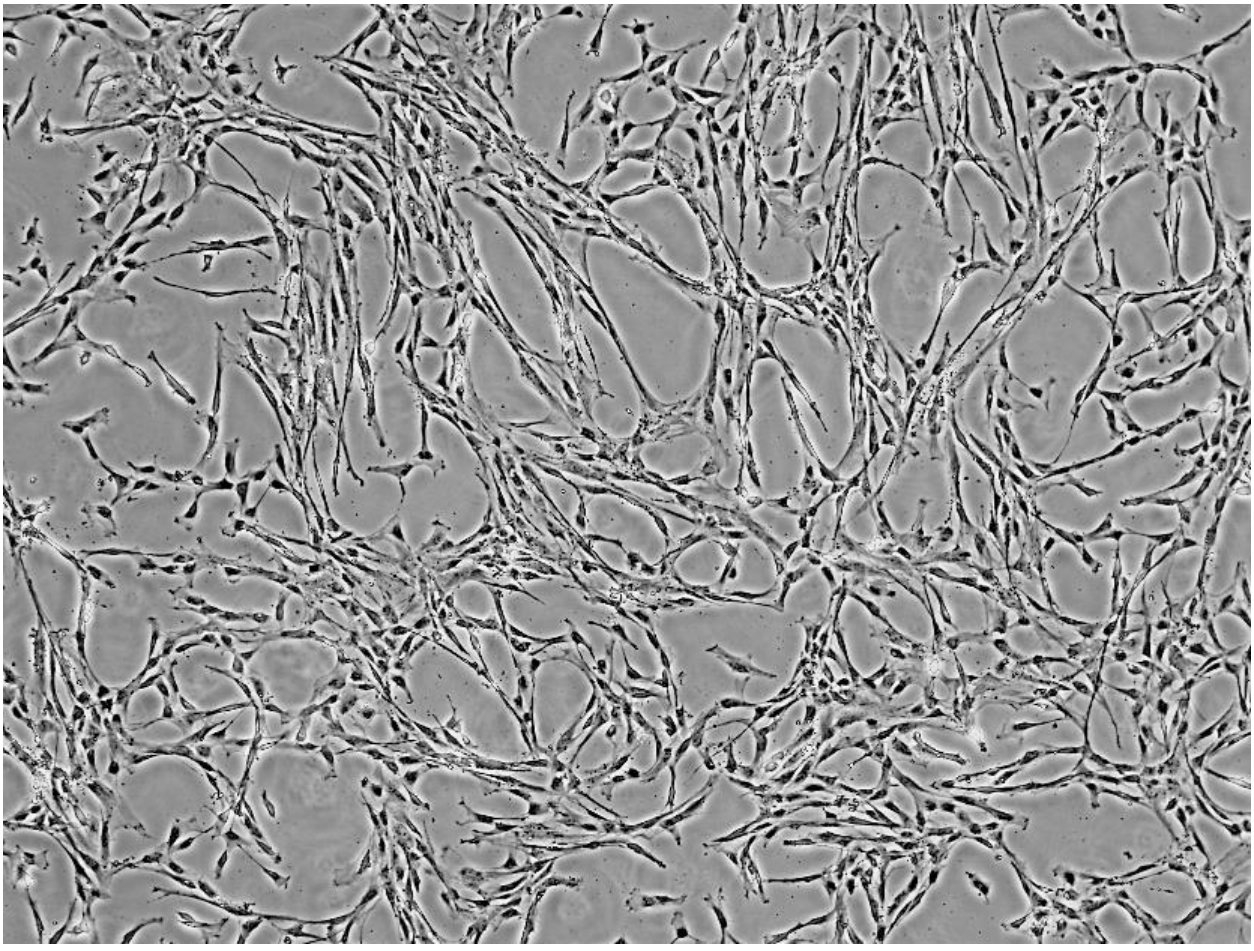

Human umbilical cord tissue MSCs at culture day 9. *MSC progenitors were isolated from donated umbilical cord tissue using enzymatic digestion and the GentleMACS Octo Dissociator. The cell suspension was filtered, washed and plated at 4,000 cells per cm^2 in a T75 tissue culture flask with MSC expansion medium (picture by Pamela Noldner, Duke University).*

What? Mesenchymal stromal cells (MSCs) are a culture adapted product with multimodal properties under investigation for a wide array of disorders. Most diseases being targeted include

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a strong inflammatory component such as graft-versus-host disease (GVHD), Crohn's disease, and COVID-19, but MSCs are also being tested for acute and chronic tissue injury syndromes such as amyotrophic lateral sclerosis (ALS), skeletal tissue damage, and ischemic heart failure (1). Despite having success in preclinical and clinical trials over the last 25 years, there remains to be a MSC product approved by the US FDA. This emphasizes the need for more robust potency markers and proper clinical trial design with biomarkers to harness the full potential of MSCs as a cell therapy product.

MSCs are cultured from vascularized tissues, such as bone marrow, perinatal tissues, and adipose tissues. Once cultured, MSCs can be driven to differentiate into multiple cell-types, which initially led to them being referred to as "stem cells." Although MSCs have multipotency potential in culture, they encompass a heterogenous population of cells that should be distinguished from pure multipotent stem/progenitor cells (which can be a subset of MSCs but lost in extended culture). MSCs isolated from different tissues or MSCs from the same tissue isolated with different manufacturing procedures can be functionally distinct (2). Further, single MSC preparations contain heterogenous cell populations highlighting the need for more stringent assays to characterize and define the potency of MSCs. In 2019, ISCT updated standards to define MSCs with additional emphasis on source tissue and a matrix of predicted functionally relevant readouts (3). It is hypothesized that the mechanism of action of MSCs is diverse, depending on the clinical target, and relates to the ability of MSCs to promote tissue repair and to modulate the inflammatory response.

Why? MSCs have an excellent safety profile and can be produced by simple manufacturing procedures. They target inflammation and cellular injury broadening their potential for treating an array of acute and chronic inflammatory disorders and tissue injury. Current indications, such as steroid-refractory acute GVHD in Pediatric Patients and perianal fistula associated with Crohn's disease, have a clear clinically unmet need.

Who? MSCs continue to draw interest from academic and commercial sectors. In the last 5 years, over 25,000 publications have been listed on PubMed and the global market size for MSCs has surpassed $200 million USD in 2021.

When? MSCs were initially described in the 1970s as adherent cells with osteogenic potential and have now become one of the most common investigational clinical products in the cell therapy space. Since the first clinical trial using MSCs in 1995 (4), there have been over 300 completed trials using MSCs for a diverse set of diseases and conditions (1).

Where? Globally, 10 MSCs therapies have been approved in Canada, Europe, South Korea, Japan, India, and New Zealand. Recently, the US FDA required further evidence from Mesoblast prior to granting approval for using the MSCs therapy remestemcel-L to treat pediatric acute GVHD. Although the Mesoblast Phase 3 trial did not meet the primary end point, promising results were found in a subset of pediatric patients. The concerns of US FDA related to having potency

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assays that more accurately correspond to clinical read outs and more rigorous trial design and interpretation of data (5).

How? MSCs have the potential to sense and respond to the microenvironment. This is advantageous over traditional therapies yet involves overcoming new challenges to developing off-the-shelf MSCs products. Current work should strive to characterize the final MSC product (define meaningful critical quality attributes) and establish more accurate and meaningful potency assays for specific indications (6). Future work should focus on enhancing subpopulations, for example extending the survival of stem/progenitor cells for tissue engineering or *in vitro* programming for specific indications, and new methods should focus on the improvement of homing MSCs to appropriate tissues and target cells (7). Ultimately, we as a field need a greater understanding of their mechanism of actions in specific clinical populations.

Did you know that… Once injected intravenously, MSCs traffic to the lung and are rapidly cleared. It's hypothesized that interactions with tissue resident cells, such as macrophages, leads to lasting effects on the host immune system (8-10).

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Keywords:

- Mesenchymal Stromal cells
- inflammation
- Graft vs Host Disease
- Crohn's disease

Brief Summary:

Since their discovery in the 1970's, MSC have been the focus of intense research in the field of regenerative medicine with some encouraging clinical data in diseases with inflammatory component. Surprisingly, there is still much to learn on their mechanisms of action.