"Periangioblasts, adult skeletal muscle stem cells for the treatment of muscular dystrophies"

Background and Description of Invention. The ideal cellular population for cell therapy of genetic and acquired diseases of striated muscle should be easily obtained from accessible anatomical sites, expandable *in vitro* to the extent required for systemic treatment of primary myopathies and highly localized (intra-coronary) treatment of cardiomyopathies. Furthermore, these cells should be able to reach the target muscle *in vivo* and should be easily transducible with viral vectors.
Mesoderm stem cells include, beside the canonical hematopoietic and mesenchymal stem cells, a number of newly described and only partially characterized stem/progenitor cells that include:

- endothelial progenitor cells (EPC)
- multipotent adult progenitor cells (MAPC),
- muscle derived stem cells (MDCS),
- side population cells (SP),
- mesoangioblasts,
- stem/progenitor cells from muscle endothelium,
- sinovia,
- dermis,
- adipose tissue.

The phenotypic complexity and the lineage relationships between these cells are to date largely unexplored, while known differences among them are based on gene expression signatures and differentiation potential spectrum.

The present invention describes the isolation of periangioblasts from biopsies of human and mouse skeletal muscle. Periangioblasts are defined as mesoderm progenitors cells derived from a sub-population of blood vessels pericytes of post-natal skeletal muscle displaying high potential of skeletal muscle regeneration. In the case of human skeletal muscle, these cells can be expanded *in vitro* for about 20 population doublings before undergoing senescence as diploid non tumorigenic cells. When transplanted into dystrophic immunodeficient mice they give rise to high numbers of new fibers expressing human dystrophin.
This is the first characterization of a human cell population that fulfils all the criteria of a successful cell therapy protocol in Duchenne Muscular Dystrophy. Moreover, the same protocol can be applied to biopsies of mouse and human cardiac muscle. Although primarily designed for muscular dystrophy, this invention may be exploited also for acquired disorders of skeletal muscle, such as sphincter lesions, hernias or, together with biomaterials, surgical ablation of small muscles.

Patent information. The international patent application was published as WO2007093412.
Patent granted in US (US8071380). Patent pending in Europe (intention to grant).

Stage of Development. Phase I/II clinical trial was carried out. Started in March 2011, at San Raffaele Hospital on paediatric patients affected by Duchenne Muscular Dystrophy (Cossu et al., *Intra-arterial transplantation of HLA-matched donor mesoangioblasts in Duchenne muscular dystrophy. EMBO Mol. Med. 2015*).

Potential Applications and Competitive Advantages. The present invention relates to skeletal muscle disorders such as Duchenne and other forms of muscular dystrophy, including but not limited to limb girdle, facio-scapulo-homeral, myotonic, Emery-Dreyfuss etc, as well as inflammatory myopathies, which may all be treated with skeletal muscle periangioblasts (*Dellavallle et al., Pericytes of human skeletal muscle are myogenic precursors distinct from satellite cells. Nature Cell Biology 2007*).

Among the critical advantages of this invention:

- Periangioblasts can be easily isolated from the very same biopsy that is used for diagnosis. In addition, a needle biopsy, which is a highly tolerable surgery, can be performed every few years to repeat the therapy protocol.
- Periangioblasts express some of the proteins that leukocytes use to adhere to and cross the endothelium and thus can diffuse into the interstitium of skeletal muscle when delivered intra-arterially. This is a distinct advantage over resident satellite cells.
- Catheter-mediated delivery to the subclavia and the iliac arteries allow periangioblasts from skeletal muscle to reach and colonize muscles essential for motility.
- Both normal and dystrophic periangioblasts maintain a diploid karyotype, are not tumorigenic in immunodeficient mice and undergo senescence after approximately 20 population doublings *in vitro*.
- When induced to differentiate *in vitro*, periangioblasts spontaneously differentiate into skeletal muscle cells with a frequency of up to 40%, an efficiency remarkably superior to any other non-myogenic cell tested thus far and second only to resident satellite cells, which however cannot be delivered through the circulation.
- Although not yet tested in a systematic comparative way, the number of dystrophin positive muscle fibers produced in vivo by periangioblasts is higher than what reported previously for other cell types (except resident satellite cells).

We seek a potential commercial partner focused on skeletal muscle disorders to further explore mammalian post-natal progenitors.

For further information on this project please contact:

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