## Stimulating Endogenous Stem Cells as a therapy for Degenerative Muscle Disease: Project making significant progress

**Paris (France), November 2011 –** A number of encouraging advances have been made by scientists from the EndoStem consortium (www.endostem.eu). This partnership is a large scale scientific collaboration coordinated by Dr David Sassoon (UPMC/Inserm, Paris, France), and co-financed by the European Commission via the 7th Framework Programme. It aims to develop new approaches for stimulating stem cells that are resident in damaged tissue, which is recognised as one of the most promising strategies, notably for degenerative diseases.

### Research Advances

#### Identifying stem cells

In a paper[1] published in the Proceedings of the national academy of Sciences, the team of Dr. Marazzi and Dr. Sassoon (Université Pierre et Marie Curie, France) in collaboration with Dr. Relaix (Université Pierre et Marie Curie, France) report the development of a model that allows them to detect cells expressing a gene known as PW1. The teams were able to easily identify stem cells in every tissue examined, including the brain and skin. This mouse model demonstrates that PW1 serves as an invaluable marker for competent self-renewing adult stem cells and promises application in fundamental research and therapeutic development, as self renewal is a critical characteristic of all stem cells.

#### Understanding muscle formation and maintenance

The balance between muscle stem cell self-renewal and differentiation is crucial during early muscle formation (myogenesis) from progenitors. Dr. Relaix's team (Université Pierre et Marie Curie, France) has shown in a study[2] published in the high impact 'Developmental Cell' journal that the neural crest cells (NCC), a cell population that gives rise to different cell lineages, is involved in regulating the commitment of skeletal muscle progenitor cells to myogenesis. The interaction between the cell types controls survival of the muscle progenitor cells and sustains them in an undifferentiated state. Essentially, understanding muscle development is pivotal to muscle regenerative medicine[3].

#### Boost for therapeutic applications of mesoangioblasts

Mesoangioblasts are a population of blood vessel-associated stem cells that have been shown to contribute to muscle repair when transplanted in dystrophic mice, dogs and are now in clinical trials in humans. A study by Dr. Brunelli's team[4] showed that the protein necdin is able to accelerate and enhance myogenic differentiation of endogenous or transplanted mesoangioblasts and to increase cell survival, thus leading to a more efficient reconstitution of the dystrophic muscle. In particular, they found that necdin acts through a transcriptional regulation of myogenin, in cooperation with a transcription factor called MyoD.

#### Cell junctions as therapeutic target

As an extension of the blood vessel work, Prof. Dejana (IFOM, Italy) has studied circulating endothelial progenitors (key maintaining cells of blood vessel integrity) and the mechanisms that induce their mobilization and migration to damaged areas. Published in PLOS One she has demonstrated that the absence an adhesion molecule of tight junctions (named JAM-A), does not modify angiogenesis[5], offering critical insight ensuring efficient nutrient supply to growing tissues.

#### A 2-step model to access target genes

Dr. Puri's group (Dulbecco Telethon Institute, Italy) unravelled the interactions between MyoD, and chromatin in undifferentiated muscle cells[6]. Indeed, the conformation of chromatin in these cells is

such that MyoD is unable to access the specific site of the chromatin to allow genes to be transcribed into proteins. Their findings revealed that a complex, allows MyoD to binds to the chromatin at a specific site. A signalling cascade then remodel the chromatin to allow the transcription machinery to access the target gene and initiate differentiation. This evidence explains the mechanism by which tissue-specific transcription factors access the chromatin at specific site previously silenced and impact the balance between stem cells and their differentiated progeny.

### New mechanism controlling inflammation and tissue repair

After injury of the skeletal muscle, specific immune cells provide the first signals to activate 'satellite' cells as part of the normal inflammation process, which should be regulated in order for the muscle to heal properly, otherwise large scar tissue forms. This phenomenom involves a transition of the immune cells from a proinflammatory state to an antiinflammatory one. Prof. Muñoz-Cánoves' team (Pompeu Fabra University, Spain) provided evidence[7] for a new role for a specific protein named MKP-1 in regulating this transition and the resolution of inflammation during muscle regeneration. The team also showed that MKP-1 is not necessary for satellite cell repair. Prof. Muñoz-Cánoves' team propose a model whereby induction of specific factors in proinflamatory cells, stimulates a signal cascade in the antiinflammatory immune cells. This offers new avenues for treating inflammatory myopathies [8], [9],[10, 11].

### Sustaining the muscle stem cell pool: Nitric Oxide in the Clinic

The muscle stem cell, becomes depleted as several rounds of regeneration occur during repetitive-acute and chronic damages such as in muscular dystrophy. Prof. Clementi's team (University of Milano, Italy) in collaboration with Dr. Brunelli (San Raffaele Scientific Institute, Italy), has clearly demonstrated, that the anti oxidant, nitric oxide stimulates muscle stem cell self renewal in such a way that it prevents the exhaustion of their reserve pool. These results[12], published in 'Stem Cells', led to the identification of molsidomine, a nitric oxide releasing drug approved for use in humans, as a potential therapeutic for muscular dystrophies.

Prof. Clementi has shown that NCX 320, a compound releasing both ibuprofen and the antioxidant nitric oxide, had significant therapeutic effects in a pre-clinical model of muscular dystrophy[13].

Little is known about the oxidative changes triggered by muscle injury and their role in the regeneration process. ROS (reactive oxygen species) generation occurs in the damaged muscle soon after injury. Dr. Brunelli found out that soon after, an antioxidant response is triggered promoting muscle regeneration[14] providing mechanistic insight to Prof. Clementi's pre-clinical work.

Importantly, and as an extension of this work, Prof. Clementi has also reported the successful outcome of a phase IIa clinical trial, which enrolled patients suffering from Duchenne, Becker and Limb Girdle dystrophies that were treated with a combination of the nitric oxide/ibuprofen[15] opening the way for effective therapeutic application.

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## Notes to editors

### *About Endostem*

EndoStem (www.endostem.eu) is a partnership of 15 research and clinical teams from globally recognised academic centres, small biotech and large pharmaceutical companies working together to develop new strategies aimed at stimulating stem cells that are resident in damaged tissue to repair it in situ. This approach is recognised as one of the most promising approaches to targeting stem cells for regenerative medicine due to the alignment with existing therapeutic development approaches used by large industry and recent advances in understanding the key barriers for tissue regeneration. Coordinated by Professor David Sassoon, co-financed by the European Commission via the 7th Framework Programme the aims of the project over are:

- Implementation of clinical trials, with muscular dystrophies as the primary clinical target using innovative biopharmaceuticals
- Development of novel best in class biopharmaceuticals with highly specific and well defined modes of action
- Fast track clinical translation based on a constant feedback loop between emerging patient responsiveness to new drugs and the development of the next generation of therapeutics
- Better understanding of the key issues preventing effective tissue repair matched with approaches to circumvent them

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