

# Joint treatment

The combined use of stem cells and a growth factor reduces disease symptoms in mice

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Periodic injections of a type of adult human stem cell in combination with daily doses of a growth factor may be a promising alternative in the treatment of progressive muscular dystrophies. Researchers from the Human Genome Research Center (HGRC) at the University of São Paulo (USP) have obtained encouraging results using this approach in muscle cells from patients with Duchenne muscular dystrophy and in mice with a congenital form of muscular dystrophy. The joint therapy used mesenchymal stem cells (MSCs) obtained from the umbilical cords of newborn infants along with doses of insulin-like growth factor 1 (IGF-1). In human tissue cultures, this therapeutic scheme increased the expression of dystrophin, a protein that is essential for maintaining the integrity of muscles. In rodents, the experimental treatment protocol reduced muscle inflammation and fibrosis, which led to an improvement in the animals' clinical condition. The results of the work were published on June 4 in the online version of the scientific journal *Stem Cell Reviews and Reports*.

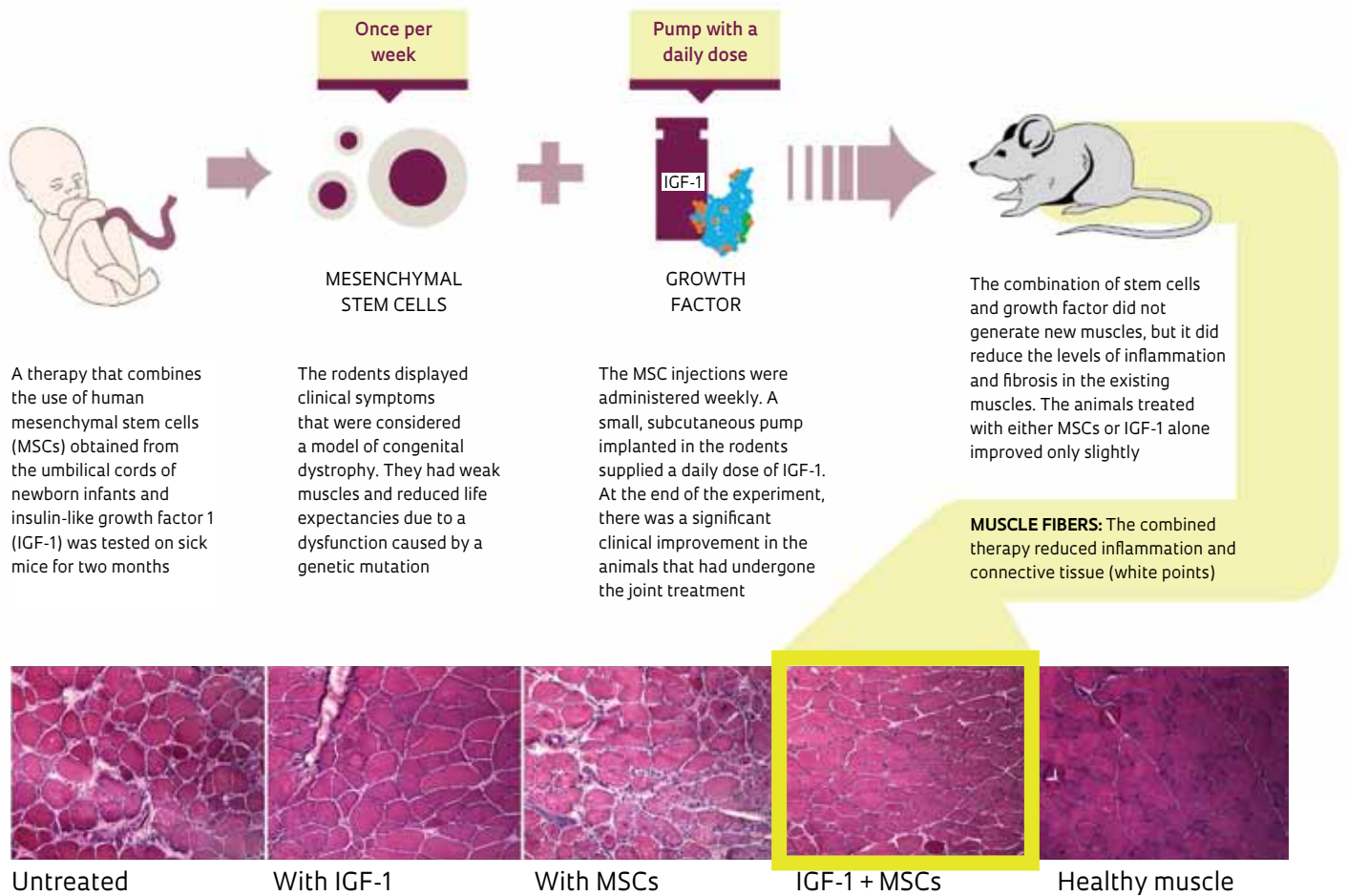
The stem-cells-plus-IGF-1 double treatment did not generate new, healthy muscles, as was expected. However, it appears to have created more favorable conditions for preserving the functionality of the already-existing musculature. Therefore, this approach could be a means of avoiding or reducing the degeneration caused by dystrophies in general. The joint therapy has an additional advantage: "Mesenchymal stem cells have immunosuppressive properties," explains

Mayana Zatz, coordinator of the team that conducted the study at the USP center, one of the Research, Innovation and Dissemination Centers (RIDC's), which are financed by FAPESP. "With these cells, we reduced the risk of the injected material being rejected," says Zatz. The immune systems of the mice in the experiment, for example, did not need to be "switched off" before the animals received the human stem cell injections.

Normally, when the donor and the recipient of tissues or cells are not the same individual, it is necessary to temporarily destroy the immune defenses of the recipient, which is always a risky procedure that leaves the patient vulnerable to external infections. If this procedure is not performed, however, the donor material will be perceived by the recipient's defenses as a potentially dangerous agent, and the implant will be fatally rejected. By using mesenchymal stem cells, rejection can apparently be avoided without the need to overrule the patient's immune system. This benefit occurs even in extreme cases, such as the experiment performed at USP, in which the recipient (mouse) and the donor (human) were members of different species.

There are indications that both components of the candidate joint therapy against dystrophy may be beneficial to muscles. Mesenchymal stem cells are largely undifferentiated and possess the capacity to generate many types of tissue, including bone, cartilage, fat cells that support blood formation and fibrous connective tissue. It is also suspected that MSCs may have a role in

# A possible therapy against dystrophy



A therapy that combines the use of human mesenchymal stem cells (MSCs) obtained from the umbilical cords of newborn infants and insulin-like growth factor 1 (IGF-1) was tested on sick mice for two months

The rodents displayed clinical symptoms that were considered a model of congenital dystrophy. They had weak muscles and reduced life expectancies due to a dysfunction caused by a genetic mutation

The MSC injections were administered weekly. A small, subcutaneous pump implanted in the rodents supplied a daily dose of IGF-1. At the end of the experiment, there was a significant clinical improvement in the animals that had undergone the joint treatment

The combination of stem cells and growth factor did not generate new muscles, but it did reduce the levels of inflammation and fibrosis in the existing muscles. The animals treated with either MSCs or IGF-1 alone improved only slightly

**MUSCLE FIBERS:** The combined therapy reduced inflammation and connective tissue (white points)

the muscle regeneration process. Among other functions, IGF-1 is involved in the development and growth of muscles. Therefore, it was logical to assess the possible effects of a therapeutic scheme using these two factors.

For 60 days, the researchers evaluated the *in vivo* effects of different treatment protocols on 46 mice with clinical symptoms similar to those of congenital muscular dystrophy. Due to a mutation in the lamina-associated polypeptide 2 alpha gene, the animals had a deficiency in the production of the merosin protein, a dysfunction that causes muscle weakness and reduces life expectancy. “They drag their back legs and have considerably reduced muscle strength,” states Mariane Secco, the biologist chiefly responsible for the human and animal experiments.

The rodents were divided into four groups: the first was not treated and functioned as a control group; the sec-

ond received only stem cell injections; the third received only doses of growth factor; and the fourth received the combined therapy. The stem cells were injected into the rodents once per week. A small, subcutaneous pump supplied a dose of two milligrams of IGF-1 per kilogram of the animal’s body weight every day. At the end of the study, a biopsy was performed on the muscle tissue, and a significant improvement was found in the animals that received the joint therapy.

Given the positive results, Zatz, Secco and their collaborators initially suspected that the IGF-1 had stimulated the MSCs to become muscle cells. However, this transformation was not detected in any of the four groups of mice. Instead, the improvement was caused by decreased levels of inflammation and muscle fibrosis, which in turn may have led to increased skeletal muscle strength in

the sick animals. Apparently, the growth factor boosts the effects of the stem cells and vice versa. “We believe that it is unnecessary for the stem cells injected into the muscle cells to differentiate in order to produce a clinical benefit,” says Zatz. The combined treatment will be tested on dogs with dystrophy to determine whether the positive results are also manifested in these animals. ■

## The Project

Human Genome Research Center no. 1998/14254-2 **Modality** Research, Innovation and Dissemination Centers (RIDC’s) **Coordinator** Mayana Zatz – IB-USP **Investment** R\$ 34,412,866.53

## Scientific article

SECCO, M. *et al.* Systemic delivery of human mesenchymal stromal cells combined with IGF-1 enhances muscle functional recovery in LAMA2dy/2j dystrophic mice. **Stem Cells Reviews and Reports**. Published online on June 4, 2012.