EMBARGO UNTIL 5:00 PM ON 9 JANUARY 2023

MULTIPLE SCLEROSIS: *NATURE MEDICINE* PUBLISHES THE RESULTS OF THE FIRST CLINICAL TRIAL IN THE WORLD WITH NEURAL STEM CELLS

A clinical trial developed and carried out by the IRCCS San Raffaele Scientific Institute opens the way for the development of innovative cellular therapy for patients with progressive forms of multiple sclerosis

Milan, 9 January 2023 (*5:00 pm embargo*) - In May 2017, for the first time in the world, a patient with advanced progressive multiple sclerosis received therapy based on neural (brain) stem cells as part of the STEMS research. The study is coordinated by professor Gianvito Martino, scientific director of the IRCCS San Raffaele Scientific Institute in Milan and Vice Chancellor of Research and the Third Mission of the Vita-Salute San Raffaele University, a pioneer of the research in this area.

Today, the results of the trial have been published in the prestigious ***Nature Medicine*** magazine: the doctors and researchers from the Neuroimmunology Research Unit and the Multiple Sclerosis Centre of the IRCCS San Raffaele Scientific Institute have demonstrated the safety and tolerability of the treatment. They observed a reduction in brain atrophy in patients treated with the largest number of neural stem cells and a variation in the pro-generative cerebro spinal fluide (CSF) profile after treatment. However, although these results are very interesting, they need to be confirmed on a larger group of patients before any possible use of these cells in clinical practice can be contemplated.

The **innovation** of this trial is the use of a new advanced cellular therapy based on neural stem cells which have never been used before in patients with multiple sclerosis. Unlike hematopoietic stem cells (used in relapsing-remitting forms of the disease but ineffective in the progressive forms) and mesenchymal stem cells (which haven't shown any benefits for patients with progressive multiple sclerosis), in preclinical research studies, these cells have demonstrated they can have a high pro-regenerative potential after transplantation.

Neural stem cells represent a **promising therapeutic strategy** for a complex and heterogeneous disease such as multiple sclerosis, where there are multiple mechanisms that contribute towards the progression of disability (from inflammation to neurodegeneration) and where action is needed to develop effective treatment.

It is above all thanks to the support of the Italian Multiple Sclerosis Association (AISM) and its Foundation (FISM) if this therapy, the fruit of 20 years of research, has reached clinical trials. *"This is an important goal for people with multiple sclerosis and their families who have supported research for all these years with patience and hope. We wouldn't have reached this far without their support. However, there is still a long way to go because there still isn't enough data available to consider this therapeutic opportunity an actual therapy*", explains professor **Gianvito Martino**.

"*The next step*", concludes Martino, "*is to go ahead with new clinical trials that involve broader groups of patients with the aim of proving the effectiveness of neural stem cells in blocking the progression of the disease as well as their ability to regenerate damaged areas of the nervous system. The final goal, which is the great challenge which we decided to take on 20 years ago, is to develop an innovative and effective therapy for people with progressive forms of MS and who, as of today, have limited therapeutic options*".

"*For over twenty years we have promoted and supported stem cell research, investing in basic research and human trials. Scientific research is a lengthy process, but it's the only way to achieve results that can tangibly change people's lives. This is the research we want and the research we fund. Over the past twenty years, a lot has changed in multiple sclerosis, and a lot is being done for the progressive forms. People with the most serious forms have innovative answers to help them deal with symptoms and have a better quality of life, also thanks to rehabilitation. We will continue to develop this stem cell research as well as other innovative projects to continue towards a world without multiple sclerosis*" states **Mario Alberto Battaglia**, Chairman of the Italian Multiple Sclerosis Foundation (FISM).

The scientific foundations of this trial have been laid down in a series of studies by Gianvito Martino's team who between 2003 and 2009 proved the efficacy of transplanting neural stem cells in numerous multiple sclerosis experimental model.

The STEMS Research

The therapy tested in the STEMS research consists in a lumbar puncture that infuses neural stem cells directly into the cerebrospinal fluid. This allows the neural stem cells to flow to the brain and spinal cord (the locations affected by multiple sclerosis) where the cells can act.

Neural stem cells are progenitor cells able to differentiate into every type of nerve cell. Animal models have shown that once these cells have been transplanted, they are able to reach cerebral and spinal cord lesions because they are attracted by damaged cells. Once the lesions have been reached, the cells promote neuroprotection and repair mechanisms, releasing immunomodulating and pro-regenerative substances.

The trial involved 12 severely disabled people with progressive MS who had already tried the currently available therapies with little or no success. The patients were divided into 4 groups, each with 3 patients, who received an increasing number of cells through a single lumbar puncture, ranging from about 50 million cells administered to the first group, to about 500 million cells administered to the last group.

The cells used for the transplant were of foetal origin and were prepared thanks to a collaboration with the *Laboratorio di Terapia Cellulare Stefano Verrio*, supported by the *Fondazione Matilde Tettamanti e Menotti De Marchi Onlus* and the *Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico*.

"*The published paper, not only demonstrates the safety and tolerability of the treatment, but also describes a significant reduction in the loss of cerebral tissue, evaluated by magnetic resonance monitoring during the subsequent two years, in the patients who received the largest number of neural stem cells. This data is supported by the analysis of the cerebrospinal fluid which highlighted a change in composition after the transplant, showing an improvement in terms of growth factors and neuroprotection substances*", explains Angela Genchi a researcher from the Neuroimmunology laboratory and author of the scientific paper.

This work has been possible thanks to the contribution of the Italian Multiple Sclerosis Foundation (FISM) and: Cariplo Foundation (Project 2010-1835 at GM), Associazione Amici Centro Sclerosi Multipla (ACeSM), BMW Italy, Fondazione Tettamanti Menotti De Marchi Onlus, Comitato Stefano Verri Onlus, Comitato Maria Letizia Verga Onlus.

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Neural stem cell transplantation in patients with progressive multiple sclerosis: An open label, phase I study - Nature Medicine 9 January 2023

Angela Genchi[1,2,3], Elena Brambilla[1], Francesca Sangalli[2], Marta Radaelli[2], Marco Bacigaluppi[1,2,3], Roberto Furlan[3,4], Annapaola Andolfo[5], Denise Drago[5], Cinzia Magagnotti[5], Giulia Maria Scotti[6], Raffaella Greco[7], Paolo Vezzulli[8], Linda Ottoboni[1], Marco Bonopane[9], Daniela Capilupo[2], Francesca Ruffini[1], Daniela Belotti[10,11], Benedetta Cabiati[10,11], Stefania Cesana[10,11], Giada Matera[10,11], Letizia Leocani[3], Vittorio Martinelli[2], Lucia Moiola[2], Luca Vago[7], Paola Panina-Bordignon[1,3], Andrea Falini[3,8], Fabio Ciceri[3,7], Anna Uglietti[12], Maria Pia Sormani[13], Giancarlo Comi[3], Mario Alberto Battaglia[14], Maria Rocca[2,3,15], Loredana Storelli[15], Elisabetta Pagani[15], Giuseppe Gaipa[10,11], Gianvito Martino[1,2,3]

[1]Neuroimmunology Unit, Institute of Experimental Neurology, IRCCS San Raffaele Scientific Institute, Milan, Italy. [2] Department of Neurology, IRCCS San Raffaele Scientific Institute, Milan, Italy. [3]University Vita-Salute San Raffaele, Milan, Italy. [4]Clinical Neuroimmunology Unit, Institute of Experimental Neurology, IRCCS San Raffaele Scientific Institute, Milan, Italy. [5]ProMeFa, Proteomics and Metabolomics Facility, Center for Omics Sciences (COSR), IRCCS San Raffaele Scientific Institute, Milan, Italy. [6]Center for Omics Sciences (COSR), IRCCS San Raffaele Scientific Institute, Milan, Italy. [7]Haematology and Bone Marrow Transplant Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy. [8]Department of Neuroradiology and CERMAC, IRCCS San Raffaele Scientific Institute, Milan, Italy. [9]Clinical Trial Center, IRCCS San Raffaele Scientific Institute, Milan, Italy. [10]M. Tettamanti Research Center, Pediatric Clinic University of Milano-Bicocca, San Gerardo Hospital, Monza, Italy. [11]Laboratorio di Terapia Cellulare e Genica Stefano Verri, ASST-Monza, Ospedale San Gerardo, Monza, Italy.[12]Department of Gynaecology IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy. [13]Biostatistics Unit, Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy. [14]Italian Multiple Sclerosis Foundation, Genoa, Italy. [15]Neuroimaging Research Unit, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan, Italy.

Information for the press:

IRCCS Ospedale San Raffaele Press Office
Tel. 0226436255/4466 - Email: ufficio.stampa@hsr.it

Unisr Press Office- Image Building
Tel. 02.89011300- Email: unisr@imagebuilding.it