UNIVERSITÀ DI MILANO
"CENTRO DINO FERRARI"
PER LA DIAGNOSI E LA TERAPIA DELLE MALATTIE
NEUROMUSCOLARI E NEURODEGENERATIVE

FONDAZIONE I.R.C.C.S. CA' GRANDA
OSPEDALE MAGGIORE POLICLINICO
FONDAZIONE DI RICOVERO E CURA A CARATTERE
SCIENTIFICO DI NATURA PUBBLICA

Gene Therapy Reverses Effects of SMARD1 in a mouse model

In a study published online March 13 in ***Science Advances*** (http://advances.sciencemag.org/content/1/2/e1500078), researchers at Centro Dino Ferrari, University of Milan, IRCCS Fondazione Ca' Granda, Ospedale Maggiore Policlinico reported a rescue of the disease phenotype in a SMARD1 mouse model following therapeutic delivery of an AAV9 construct encoding the wild-type *IGHMBP2* via systemic injection to replace the defective gene. SMARD1 is a genetic cause of childhood death, likely underestimated as frequency. It is a neuromuscular disease characterized by degeneration of motor neurons, resulting in progressive muscular atrophy, weakness and respiratory failure due to diaphragmatic impairment. It is the second most frequent anterior horn cell diseases in infants with a known genetic cause, after SMA5q. There is no effective treatment or cure for this disease. The ideal therapeutic approach for SMARD1 and likely other genetic motor neuron diseases will be resolving the genetic defect with gene therapy.

The principal investigator of the research is Prof. Stefania Corti, MD, PhD, associate professor of neurology, principal investigator of the Neural Stem Cell Laboratory in the Neuroscience Section, Department of Pathophysiology and Transplantation. The research group included also members of her lab and researchers of the Centro Dino Ferrari, University of Milan, IRCCS Fondazione Ca'Granda, Ospedale Maggiore Policlinico.

Dr. Monica Nizzardo, the first of author of the paper, and colleagues demonstrated the efficacy of gene therapy for SMARD1, a strategy that may represent a novel and successful therapeutic approach. They described the most effective rescue of SMARD1 mice achieved with a therapeutic treatment to date; this rescue was characterized according to motor function, neuromuscular physiology, and survival after a single injection of AAV9-*IGHMBP2 in a mouse model of SMARD1.* They systemically administered AAV9 vectors encoding human wild-type *IGHMBP2*, exploiting the cutting-edge finding that AAV9 can cross the blood-brain barrier and successfully transduce the CNS. These results were

obtained in the *nmd* mouse model, which recapitulates many disease features of SMARD1 patients, with an early administration after birth. Our study verified that the reconstitution of IGHMBP2 levels in the CNS and in systemic organs corrected the pathological manifestations in these organs. More strikingly, the longest extension in survival ever reported for the *nmd* mouse model was achieved in this study (increasing survival by 450%); furthermore, the phenotype of AAV9-*IGHMBP2*-treated *nmd* animals was nearly indistinguishable from that of their wild-type littermates.

To test this strategy in a human model, they transferred wild-type *IGHMBP2* into human SMARD1 induced pluripotent stem cell-derived motor neurons; these cells exhibited increased survival and axonal length in long-term culture.

This research provides significant basic and preclinical data that could translate into clinical trials in patients with these pathologies. This study confirms the feasibility of AAV-based technologies as effective therapeutic strategies for the treatment of genetic motor neuron diseases. In particular, our results provide proof-of-principle of the feasibility of clinical translation of this strategy to treat SMARD1 and other genetic motor neuron disorders.

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For further information

Dr. Monica Nizzardo
Centro Dino Ferrari, University of Milan,
IRCCS Fondazione Ca' Granda, Ospedale Maggiore
Tel. +3902 55033833
monica.nizzardo1@gmail.com

Prof. Stefania Corti
Centro Dino Ferrari, University of Milan,
IRCCS Fondazione Ca' Granda, Ospedale Maggiore
Tel. +3902 55033817
stefania.corti@unimi.it

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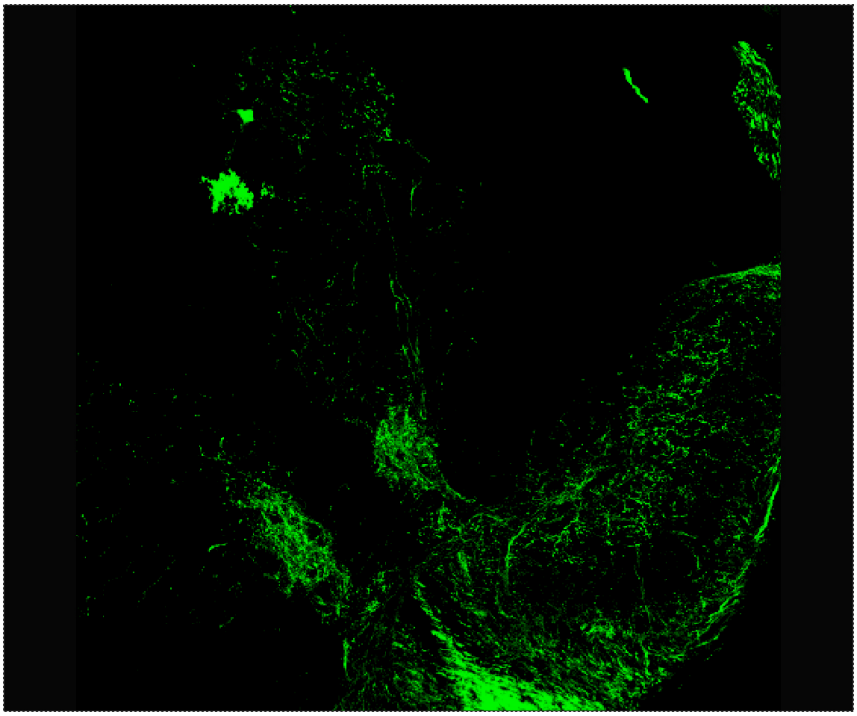

Figure legend: University of Milan scientists demonstrated the rescue of the disease phenotype in a SMARD1 mouse model following therapeutic delivery of an AAV9 construct encoding the wild-type IGHMBP2 via systemic injection to replace the defective gene.
Systemically injection of AAV9-GFP in wild-type and SMARD1 animals resulted in GFP expression (green) within the spinal cord. The transduced cells express the GFP indicating an efficient transduction of the Central Nervous System. Nizzardo et al., Science Advances March 13 2015

DIRETTORE PROF. NEREO BRESOLIN
Via F. Sforza, 35 - 20122 Milano – Tel. 02.5503.3809 - Fax 02.503.20448
E-mail: nereo.bresolin@unimi.it - centro.dinoferrari@policlinico.mi.it - www.centrodinoferrari.com