No 1 – Spring 2018

RESSTORE
Regenerative Stem Cell Therapy for Stroke

RESSTORE NEWSLETTER

Editorial

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RESSTORE is a challenging European project to develop reparative medicine for stroke patients. Improving patients' recovery requires experts of cell therapy products, neurosciences, and stroke neurology. Innovative multimodal MRI and statistics also increase our knowledge about stroke pathophysiology and treatment effects.
While we have just obtained the regulatory and ethics approval, we will start the clinical trial in the next weeks.
It is our pleasure to present here the first RESSTORE newsletter on behalf of the European consortium including France, Spain, Finland, Czech Republic and UK.

What is RESSTORE?

RESSTORE is funded by the European Commission H2020 programme.

RESSTORE is a **translational project** that will provide through a **European multicentre randomised clinical study**, essential information on **safety and efficacy** of **intravenous cell therapy** i.e. delivery of allogenic adipose tissue derived stem cells (ADSCs) in stroke patients. The objective is to improve brain repair and recovery after **ischemic stroke**.

Key information

Project dates
2015-2020
Coordination
Grenoble Alpes University, France
29 partners
from 5 countries
Budget: 6.3 M€

RESSTORE Team at the 2nd Annual Meeting
6th & 7th November 2017 in Seville, Spain

Conferences & Events

- **16-18/05/2018** - **ESOC** - 4th European Stroke Organisation Conference, Gothenburg (Sweden)
- **16-19/06/2018** - **EAN** - 4th Congress of the European Academy of Neurology, Lisbon (Portugal)
- **07-11/07/2018** - **11th FENS** Forum of Neuroscience, Berlin (Germany)
- 23-24/10/2018 - RESSTORE 3rd Annual Meeting, Paris (France)
- **03-07/11/2018** - **SFN** - Society for Neuroscience, San Diego (USA)

Want to know more?
Visit our website:
resstore.eu
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Horizon 2020 is the **biggest EU Research and Innovation programme** ever with nearly **€80 billion** of funding available over **7 years** (2014 to 2020) - in addition to the private investment that this money will attract. It promises more **breakthroughs**, **discoveries** and **world-firsts** by taking great ideas from the **lab to the market**.

Publications

1. M. Hommel, O. Detante, I. Favre-Wiki, E. Touzé, A. Jaillard. How to measure recovery? Revisiting concepts and methods for stroke studies. Translational Stroke Research 2016
2. O. Detante, K. Muir, J. Jolkkonen. Cell Therapy in Stroke - Cautious Steps towards a Clinical Treatment. Tranlational Stroke Research 2017
3. O. Detante, J. Papassin, C. Rome. How to use stem cells for repair? Rev Neurol 2017
4. O. Detante, A. Jaillard, M. Hommel. Controlled clinical trials of cell therapy in stroke: meta-analysis at 6 months after treatment. Int J Stroke 2017
5. Rodríguez-Frutos B, Otero-Ortega L, Gutiérrez-Fernández M, Fuentes B, Ramos-Cejudo J, Díez-Tejedor E. Stem Cell Therapy and Administration Routes After Stroke. Transl Stroke 2016
6. Gutiérrez-Fernández M, Otero-Ortega L, Ramos-Cejudo J, Rodríguez-Frutos B, Fuentes B, Díez-Tejedor E. Adipose tissue-derived mesenchymal stem cells as a strategy to improve recovery after stroke. Expert Opin Biol Ther. 2015
7. Gutiérrez-Fernández M, Rodríguez-Frutos B, Ramos-Cejudo J, Otero-Ortega L, Fuentes B, Vallejo-Cremades MT, Sanz-Cuesta BE, Díez-Tejedor E. Comparison between xenogeneic and allogeneic adipose mesenchymal stem cells in the treatment of acute cerebral infarct: proof of concept in rats. J Transl Med. 2015

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 681044

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Dr Jukka Jolkkonen
WP7 Leader
University of Eastern Finland (UEF)

RESSTORE WP7 - Helping interpretation of patient data

Experimental research is indispensable to broaden our understanding on brain pathology and repair and in exploring mechanisms of promising new therapies.

Stroke is not exception in this rule. Clinical studies are hampered by patient heterogeneity including infarct size and location, co-morbidities, medication and rehabilitation that are difficult or even impossible to control. In experimental models these can be addressed one by one.

RESSTORE project was one of the first funded Horizon2020 projects. The aim is to study therapeutic effects of adipose tissue derived mesenchymal stem cells (ADSCs) in stroke patients. **What makes RESSTORE a unique project is combination of preclinical and clinical approaches.** The same cell product will be tested in stroke patients and in animal models.

WP7 is for experimental and translational studies. Partners from Finland, Spain and France investigate possible interactions between cell therapy and rehabilitation and co-morbidities, namely hypertension and diabetes. The experimental part of the project started in late 2015. Although last experiments are still ongoing, a few major findings can be shortly summarized.

Brain ischemia was produced in rats by permanent occlusion of the distal middle cerebral artery. This mimics a cortical stroke in patients. ADSCs were infused intravenously 48 h after ischemia in rats with rehabilitation or co-morbidities. Subsequently functional impairment and recovery was assessed using multiple sensitive behavioral tests. After the follow-up the animals were perfused for a detailed histological examination.

Behavioral data showed that cell therapy had a significant effect on functional outcome, which was further improved by concomitant rehabilitation (Figure 1). The strong message from this is that **nature and quantity of rehabilitation should be carefully monitored in RESSTORE clinical trial.**

Regarding hypertension and diabetes the most striking finding was exaggeration of neuroinflammation in the cortex next to the infarct. More importantly, **cell therapy efficiently decreased staining for inflammation both in rats with and without co-morbidities (Figure 2). This support the idea that cells may act through reducing neuroinflammation.**

Taken together, with minimal funding WP7 has produced valuable insight to help in interpretation of results from clinical trial. **All data so far support safety of ADSCs**. In addition, **rehabilitation and co-morbidities are important factors possibly affecting treatment effects**. The results will be presented in scientific meetings and published in Open Access journals, which are scientifically high in quality.

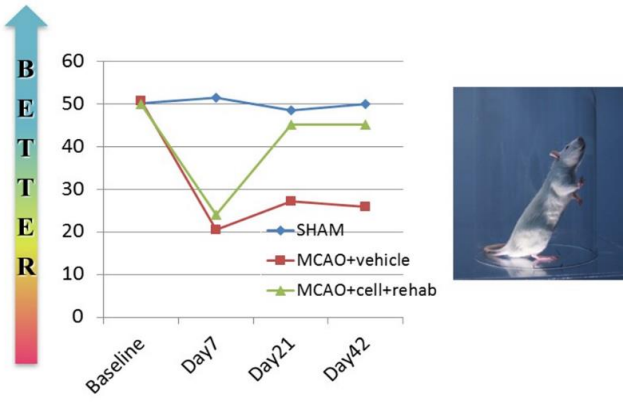

Figure 1. Spontaneous forelimb use (cylinder test) was used to assess treatment effects. Use of paralyzed forelimb was impaired after stroke but recovered almost completely by the end of the 42-day follow-up in rats receiving combined cell therapy and rehabilitation.

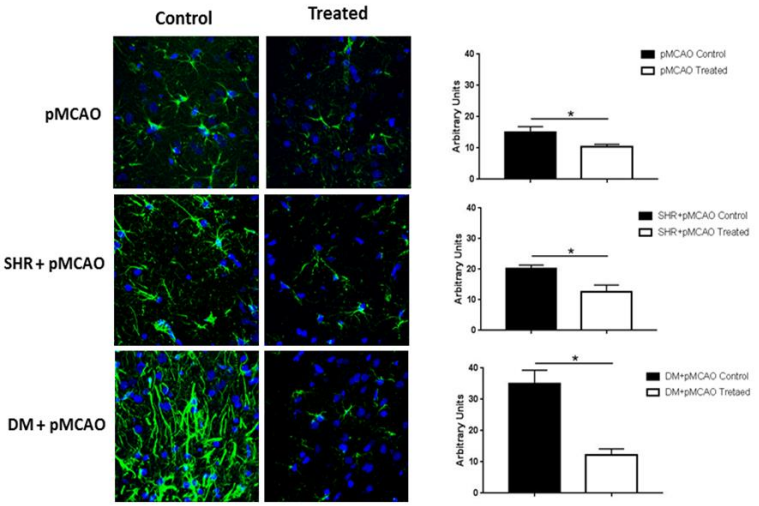

Figure 2. Semiquantitative analysis of immunostaining for perilesional inflammation (GFAP) from rats with hypertension (SHR) or diabetes (DM) subjected to cerebral ischemia (pMCAO) and treated with cells (ADSCs). ADSCs significantly reduced inflammation in experimental animals with or without co-morbidities.

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