



Esperite (ESP), The Cell Factory demonstrate anti-inflammatory mode of action of CF-MEV-117 extracellular vesicle drug candidate for Epilepsy

Esperite's (Euronext: ESP) biotech subsidiary The Cell Factory develops extracellular vesicles (EVs) biologic drug (CF-MEV-117) for treatment of drug-resistant epilepsy in children. The consortium sponsored by The Cell Factory have achieved an important milestone in the CF-MEV-117 drug development confirming an anti-inflammatory and immunosuppressive activity of the CF-MEV-117 in a dose response manner. Full results will be presented during the International Society for Extracellular Vesicles (ISEV) meeting in Toronto, Canada from 18-21 May, 2017.

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The Cell Factory, a company of Esperite Group in collaboration with Bambino Gesù Children's Hospital in Rome, Mario Negri Institute for Pharmacological Research in Milan and Women's and Children's Health Department of the University of Padua are developing the EVs drug candidate (CF-MEV-117) for treatment of drug resistant epilepsy in children.

The consortium is investigating the immunomodulatory properties of EVs derived from MSCs in several in vitro and in vivo models. It has been demonstrated by independent research groups that inhibitory effects of MSCs on human leukocytes was mediated by secreted EVs. Subsequently, it was demonstrated by our partners that MSC-derived EVs were responsible for inhibition of B-cell proliferation and differentiation and activation of T-cell apoptosis (Budoni et al., 2013; Del Fattore et al., 2015). These results have been recently confirmed with the CF-MEV-117 drug candidate manufactured by The Cell Factory. Preclinical and clinical study demonstrate that brain inflammation could be responsible for severe epileptic seizures. Pro-inflammatory molecules secreted by the stimulated glial cells are responsible for a status epilepticus. Therefore, immunomodulatory and anti-inflammatory treatment focused on astrocytes and microglia cells are reducing or eliminating symptoms of epilepsy and can prevent a relapse of the disease in the future. The project is investigating anti-inflammatory and anti-epileptic effect of the CF-MEV-117 drug candidate in both an acute phase of epilepsy and preventing development of a chronic disease. In addition, we expect that CF-MEV-117 will demonstrate much broader therapeutic effect in neurology influencing

neural cells apoptosis, neurons hyperexcitability, and neurogenesis process leading to faster brain regeneration. This will allow using the MSC-derived EVs in treatment of unmet medical needs e.g. stroke, TBI, spinal cord injury. EVs stability and small size are the key advantages allowing their immediate use in acute injuries and the drug penetration through the blood brain barrier.

CF-MEV-117 is produced using a proprietary technology developed by The Cell Factory for a large-scale production of ultra-pure EVs, using fully defined, serum-free, xeno-free culture media with no use of animal-derived components and human platelet lysates at any stage of the production process. Production is performed in a closed and scalable stirring bioreactors including a downstream processing based on the integrated sequential filtration system. EVs are continuously secreting by expanded MSCs allowing multiple harvests during one production cycle. This approach significantly reduces the contamination risk, production time, staff, GMP labs use and the cost of goods. Effectively the production of the single EVs dose is now up to 10 times cheaper when comparing to the allogenic MSCs dose equivalent. CF-MEV-117 product is sterilised by filtration during production process what is not possible for any cell therapy products (ATMPs). CF-MEV-117 product has very high batch-to-batch reproducibility. Product analysis is performed using broad range of state-of-the-art techniques i.e. NTA, immunophenotyping, proteomics, among others. Several surface markers have been analysed for CF-MEV-117 product including the tetraspanin transmembrane proteins characteristic for EVs (CD9+, CD63+ and CD81+). Interestingly, CF-MEV-117 EVs do not express HLA-ABC and HLA-DRPQ what increases the drug's safety in human use.

The consortium is fully focused on demonstration of the CF-MEV-117 product's anti-inflammatory and immunosuppressive activity and its mode of action. For that purpose T-cells and B-cells have been isolated from human peripheral blood and the cells were stimulated using anti-CD3/CD28 and CpG, respectively. CF-MEV-117 product has increased the activated T reg proliferation and effectively the T reg / T eff ration. In addition, reduction of the activated B cells proliferation and plasma cell differentiation have been observed in response to CF-MEV-117. This confirms previous results obtained using the research-grade EVs. It is worth stressing that the experiments were performed in parallel with the MSCs used for the CF-MEV-117 production. The results have confirmed the same anti-inflammatory effect of the MSCs and the MSC-derived EVs (CF-MEV-117) on stimulated human leukocytes. The CF-MEV-117 drug's effect was observed in a dose responsive manner. The next step is confirmation of the CF-MEV-117 in in vivo models before the clinical translation.

EVs including exosomes are nanometre-size, natural biological particles secreted by different types of cells in vivo and in vitro. They contain proteins, growth factors, mRNA and other molecules responsible for the therapeutic effect of MSCs. In addition, EVs have several advantages over allogenic MSCs e.g.: up to 10-times lower production costs, no risk of uncontrolled proliferation and differentiation, lower risk of immune response and easy and safe delivery into different tissues and organs in vivo. High stability allows for easy transport and storage of the "ready-to-use" products.

CF-MEV-117 drug candidate: Acute and chronic drug-resistant epilepsy

The Cell Factory is developing MSC-EVs drug candidate (CF-MEV-117) for treatment of untreatable-yet acute and chronic drug-resistant epilepsy. Epilepsy carries significant detrimental effects on the quality of life and can lead to a secondary brain damage. The disease can have different etiology, including stroke, brain trauma, and neuro-inflammation.

Epidemiology and market size (CF-MEV-117)

Epilepsy is one of the most common brain diseases affecting about 1 in 100 children under 17-year old according to CDC. Severity of the seizures is variable and the antiepileptic drugs are effective only in about 2/3 of the patients. CDC estimated annual costs related to epilepsy exceeds 15 billion USD in the United States alone.

It is expected that EVs products will be effective in treatment of other neuroinflammatory-related injuries of central nervous system. Moreover, EVs will be able to target an acute diseases i.e. TBI, brain stroke, spinal cord injury, more effectively when comparing to allogenic MSCs, due to the EV's stability and easier administration at shorter time what is critical for successful therapy. Diseases of central nervous system are among most devastating for patients and their relatives. Neurological disorders are generating a significant additional cost related to hospitalisation, rehabilitation, often eliminate the patients and their relatives from a job market. CDC estimated that annual costs related to epilepsy exceeds 15 billion USD in the United States alone with 50 million patients worldwide (WHO). Cost related to brain stroke in the United States is estimated to 34 billion USD per year (CDA), with 15 million new patients worldwide each year (WHO). Cumulative cost related to traumatic brain injury (TBI) and spinal cost injury in the United States is over 80 billion USD per year (CDA and AANS), with up to 0.5 million new incidents of spinal cord injury and 10 million of TBI per year (WHO). Most of these diseases have no effective therapy yet.

The consortium led by Esperite's The Cell Factory is gathering the leading teams in paediatric regenerative medicine, neurology, gastroenterology, immunology and EVs science. The CF-MEV-107 product is developing in collaboration with Professor Maurizio Muraca's team at the Department of Women's and Children's Health at the University of Padova in Italy. The CF-MEV-117 product is developing in collaboration with Professor Federico Vigeveno and Dr Alessandra Fierabracci team at Bambino Gesù Children's Hospital in Rome, Italy and with Dr. Annamaria Vezzani at Mario Negri Institute in Milan, Italy.

Frederic Amar, CEO: "The Cell Factory is focused on development, clinical translation and commercialization of the advanced extracellular vesicles (EVs) biologic drugs and autologous stem cell therapies. The Cell Factory goal is to master the development and production of extracellular vesicles drugs in treatment of different indications."

ESPERITE Group, listed at Euronext Amsterdam and Paris, is a leading international company in regenerative and predictive medicine established in 2000.

The Cell Factory is a biotech company, a subsidiary of the Esperite group, developing highest quality therapeutic tools for affordable regenerative medicine. The Cell Factory led by Dr. Marcin Jurga is focused on development, clinical translation and commercialization of the advanced extracellular vesicles (EVs) biologic drugs and autologous stem cell therapies. The Cell Factory goal is to become a leader in development and production of extracellular vesicles drugs in treatment of different indications i.e. graft versus host disease (GvHD) after solid organ and cell transplantations, arthritis, multiple sclerosis, cystic fibrosis, stroke, traumatic brain and spinal cord injury, newborn encephalopathy, and type 1 diabetes among others.

The Cell Factory focuses on development of the selected EVs drug candidates from a TRL 4 (non-GLP POC) until TRL 6-7 (Clinical phase II). The Cell Factory is looking for partners and investors who are interested in a rapidly growing, disruptive technology of EVs biological drugs. We are looking for different collaboration models including out-licencing, technology transfer and joint venture product development and dilutive investments.

The Cell Factory owns the full rights of a broad international patent family enabling MSC-derived extracellular vesicles (EVs) use in treatment of autoimmune, chronic and acute inflammatory diseases. The patents have been already granted in Europe and recently in China. The Cell Factory is developing the EVs biologic drug products for multiple indications in immunology, neurology and gastroenterology. The leading products are CF-MEV-107 for treatment of Crohn's disease (drug resistant perianal fistulae) and CF-MEV-117 for treatment of drug resistant epilepsy in children. The CF-MEV-107 product is ready for clinical translation and the consortium of leading academic and clinical teams sponsored by The Cell Factory is preparing the CF-MEV-107 product for first in man clinical translation in 2017.

To learn more about ESPERITE Group, or to book an interview with CEO Frederic Amar: +31 575 548 998 - ir@esperite.com or visit the websites at www.esperite.com, www.cell-factory.com, www.cryo-save.com and www.genoma.com.