



Esperite Group with The Cell Factory expands its Extracellular Vesicles product portfolio of anti-inflammatory drugs with a fourth indication : Bronchopulmonary Dysplasia.

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The Cell Factory in collaboration with the University of Padova, Italy has completed pre-clinical in-vivo tests of the CF-MEV-132 drug candidate for the treatment of bronchopulmonary dysplasia (BPD). BPD is a severe disease of the respiratory system which occurs in approximately 30% of preterm born children below 30 weeks of gestation. CF-MEV-132 has shown safety and efficacy in reducing lung damage in the rat model of hyperoxia-induced BPD. Since these severely sick babies are all intubated at birth, efficacy in experimental animals was demonstrated by administering the EVs via the intra-tracheal route, thus avoiding the risks associated with systemic administration. The Cell Factory is now preparing the CF-MEV-132 drug candidate for clinical tests in humans.

Bronchopulmonary dysplasia (BPD) is a severe disease of the respiratory system which occurs in app. 30% of preterm born children (below 30 weeks of gestation). Incidents of BPD are correlated with the low gestational age at birth, and over 90% of extremely immature babies are affected by the disease. The lungs of the babies affected with BPD are not properly developed and the patients require oxygen therapy and intensive care immediately after birth. BPD has severe long-term consequences for the patients, and the disease is responsible for the major cause of death in the first month of life in developed countries.

Current treatment of BPD is focused on mechanic ventilation and oxygen therapy immediately after birth and supplementation of surfactant. Mechanic ventilation and oxygen treatment lead to hyperoxia and severe inflammation damaging lungs. In consequence, inflammation prevents the development of the lungs, and cause a significant reduction in lung surface, lower number of alveoli and impaired lung vascularization. Effectively lungs cannot provide a sufficient amount of air to the organism what results in impaired development and metabolic functions of the entire organism.

Our approach is focused on using CF-MEV-132 drug candidate (extracellular vesicles derived from mesenchymal stem cells) to inhibit lung inflammation and improve the regeneration process in preterm babies with BPD. CF-MEV-132 treatment will be supplementary to the life-saving therapies, i.e. oxygen treatment, ventilation, and surfactant treatment.

CF-MEV-132 drug candidate belongs to the CF-MEV family of anti-inflammatory EV drugs produced by The Cell Factory. CF-MEV drugs share the mode of action targeting both innate and acquired immune systems. All CF-MEV drugs are manufactured using The Cell Factory proprietary EVs technology platform. The efficacy of CF-MEV-132 drug candidate was investigated by The Call Factory in collaboration with The Human Anatomy Section, Department of Neurosciences, The Neonatal Intensive Care Unit, and the Stem Cell and Regenerative Medicine Laboratory of the Department of Women's and Children's Health, Department of Cardiac, Thoracic and Vascular Sciences of the University of Padova and Pediatric Clinic and Institute of Pediatric Research, Città della Speranza, Padova, Italy. The experimental results of the pre-clinical study on CF-MEV-132 drug candidate were recently published by Porzionato et al. in *Am J Physiol Lung Cell Mol Physiol*. 2018 Oct 4 (reference: 1). The study was performed using a rat model of hyperoxia-induced BPD. EVs were injected intratracheally to demonstrate efficacy with the non-invasive method of drug administration. This approach could significantly reduce the risk of future therapy of newborn preterm children with BPD. Histomorphometric

analysis of the lungs showed significant reduction of organ injury in the animals treated with CF-MEV-132 compared with sham-treated controls, i.e. increased total number of alveoli and decreased mean alveolar volume. In addition, EVs treatment prevented an increase in medial thickness of small pulmonary vessels, a sign of pulmonary hypertension associated with BPD development. No adverse effects were observed after administration of CF-MEV-132. The study demonstrated that EVs can reduce hyperoxia-induced lung damage and can be safely delivered via the intratracheal route into patients.

Mode of action of The Cell Factory's EVs drug candidates is focused on immunomodulation and suppression of the innate and acquired immune systems. In collaboration with our academic and clinical partners, we have demonstrated that CF-MEVs drug candidates suppress B cell proliferation, differentiation and antibody production. CF-MEVs induce apoptosis of activated conventional T cell and induce regulatory T cells increasing the Treg/Teff ratio.

Other experiments have demonstrated that co-culture of EVs (CF-MEVs drug candidates) with PBMCs resulted in significant reduction of degranulating NK cells (CD56+ CD107a+). Exposure of K562-stimulated PBMCs to EVs induced a significant reduction of CD56+ IFN- γ + cells compared to co-culture with parental MSCs. (references: 2,3,4,5). In vitro data have been confirmed in several in vivo models. For example, EVs were injected intraperitoneally into a mouse model of DSS-induced ulcerative colitis. EVs treatment showed improved disease activity index and less severe reduction in colon length. RT-PCR of colon tissue demonstrated a significant reduction of IL-1 β and COX2 in EVs treated animals. Subsequent in vivo study demonstrated an enhanced anti-inflammatory effect of 2nd generation EVs-Annexin. (references: 6,7).

Technology. The Cell Factory has developed a proprietary technology of large-scale production of ultra-pure EVs according to GMP guidelines, using fully defined, serum-free, xeno-free defined 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 bioreactor including a downstream processing based on the integrated sequential filtration system. The Cell Factory set up new standards in drug production where 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 a production of a single EVs dose is now up to 10 times cheaper when comparing to the allogenic MSCs dose equivalent, and these costs will be further reduced in the future. Closed and semi-automated production system, fully defined culture

media and ISO/GLP based quality assurance system facilitates a technology transfer what is expected in collaboration with the international partners. The EVs will become soon a viable alternative to many allogenic stem cell therapies soon and will be able to target niche indications beyond the scope of current cell therapies, i.e. immediate anti-inflammatory interventions in neurology.

EVs including exosomes are nanometer 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 the immune response, penetration through the blood-brain-barrier 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” EVs products.

Intellectual properties. The Cell Factory, a company of Esperite Group owns the full rights of a broad international patent family enabling MSC-derived extracellular vesicles (EVs) use in the treatment of autoimmune, chronic and acute inflammatory diseases. The patents have been already granted in Europe, China and recently in Canada. The Cell Factory is developing the EVs biologic drug products for multiple indications in immunology, neurology, gastroenterology and respiratory diseases. The leading products are CF-MEV-107 for treatment of Crohn’s disease (drug-resistant perianal fistulae), CF-MEV-117 for treatment of drug-resistant epilepsy in children, CF-MEV-126 for treatment of acute stroke-induced inflammation, and CF-MEV-132 for treatment of bronchopulmonary dysplasia in prematurely born children.

The Cell Factory is looking for investors and research collaboration opportunities to continue development of the EVs drug products and manufacturing technology.

Dr. Marcin Jurga, CSO at The Cell Factory, said: “Recent results of the EVs use in treatment of BPD confirm the efficacy of the CF-MEV drug family and the quality of the EVs technology developed by our Company. This significant step was possible thanks to the commitment of our research partners at the Padua University. We expect that these new evidences of the EV activity will encourage investors to support our company with the aim to develop EV immunotherapeutics for unmet medical needs.”

The Cell Factory's product portfolio:

CF-MEV-107: Crohn's disease

Inflammatory bowel disease (IBD) encompasses a spectrum of diseases affecting the gastrointestinal tract. The most common are Crohn's disease and ulcerative colitis. IBD is a chronic and often recurring inflammation of the intestines with unknown cause and limited treatment options. In the most severe cases of Crohn's disease, the patients suffer from perianal fistulas that significantly affect regular activity and may lead to complications such as an increased risk of cancer and life-threatening systemic inflammation. In Europe, the current treatment of Crohn's disease is focused on anti-TNF-alpha therapy whereas anti-integrin biologics are an alternative available in the US. Perianal fistulas often do not respond to these systemic treatments. Several clinical trials are ongoing to target perianal fistulas using allogeneic mesenchymal stem cells (MSCs) with very positive results.

Epidemiology and market size (CF-MEV-107). IBD affects 0.5% of the western countries population and this number is rapidly increasing. There are over 0.5 million people in the US, and over 1 million in Europe with Crohn's disease, with over 10 new cases per 100.000 people every year. The annual cost of therapy exceeds 5 billion USD in the US only (CDC). Up to 50% of Crohn's disease patients are affected with difficult to treat perianal fistulas, and 75% require surgery (according to CDC) what estimates the potential market size of the CF-MEV-107.

CF-MEV-132: Bronchopulmonary dysplasia

Bronchopulmonary dysplasia (BPD) is a severe disease of the respiratory system which occurs in preterm born children (below 30 weeks of gestation). The lungs of the babies affected with BPD are not properly developed and the patients require oxygen therapy and intensive care immediately after birth. BPD has severe long-term consequences for the patients, and the disease is responsible for the major cause of death in the first month of life in developed countries.

Current treatment of BPD is focused on mechanic ventilation and oxygen therapy immediately after birth and supplementation of surfactant. Mechanic ventilation and oxygen treatment lead to hyperoxia and severe inflammation damaging lungs. In consequence, inflammation prevents the development of the lungs, a significant reduction in lung surface, lower number of alveoli and impaired lung vascularization. Effectively lungs cannot provide a

sufficient amount of air to the organism what results in impaired development and metabolic functions.

Our approach is focused on using CF-MEV-132 drug candidate (extracellular vesicles derived from mesenchymal stem cells) to inhibit lung inflammation and improve the regeneration process in preterm babies with BPD. CF-MEV-132 treatment will be supplementary to the life -saving therapies, i.e. oxygen treatment, ventilation, and surfactant treatment.

Epidemiology and market size (CF-MEV-132). Bronchopulmonary dysplasia occurs in app. 30% of preterm born children (below 30 weeks of gestation). Incidents of BPD are correlated with the low gestational age at birth, and over 90% of extremely immature babies are affected by the disease. The costs related to BPD are significant and spread over the lifetime of patients affected by the disease. It has been estimated that the average hospitalisation time of a premature infant with BPD is in average 94 days and the annual cost per patient ranges from 400.000 USD to over 700.000 USD (reference: 9).

CF-MEV-117: 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 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. The 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.

CF-MEV-126: Stroke

Stroke is one of the most devastating and still incurable diseases. Brain damage following stroke is correlated with the inflammation which plays a key role in the brain's response to a stroke incident. New generation EVs drugs are containing an additional genetic cargo (miRNAs) or have bound surface molecules (i.e., Annexin V) to enhance their anti-inflammatory and neuroprotective properties.

EVs stability and small size will allow using the CF-MEV-126 drug outside the hospital immediately after the stroke incident what reduces the brain damage and improves the

recovery process. Another advantage of the EVs, when comparing to MSCs and other cell therapies, is their penetration through the blood-brain barrier what is crucial for any effective treatment targeting the central nervous system.

Epidemiology and market size (CF-MEV-126). Diseases of the central nervous system are among the 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.

Stroke is the second leading cause of disability in Europe, and 10-35% of these patients die within 28-30 days. Current stroke therapy is very limited and focused on general care and rehabilitation. In the EU 27 countries, the annual cost of stroke is estimated to €27 billion (WHO). The number of stroke events in Europe is projected to rise from 1.1 million in 2000 to 1.5 million per year by 2025 due to the aging population.

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About ESPERITE

ESPERITE is a diversified biotech global group leader in regenerative and precision medicine. Established in 2000, the holding group is headquartered in the Netherlands, listed at Euronext Amsterdam and Paris and operational in over 30 countries.

ESPERITE transforms the power of state-of-the-art technologies and scientific advancements into high quality products that bring the future of medicine to customers today at an affordable price.

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 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. inflammatory diseases, 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.

To learn more about the *ESPERITE* Group, or to book an interview with CEO Frédéric Amar: [+31 575 548 998](tel:+31575548998) - ir@esperite.com or visit the websites at www.esperite.com and www.cell-factory.com.

This press release contains inside information as referred to in article 7 paragraph 1 of Regulation (EU) 596/2014 (Market Abuse Regulation).