Esperite (ESP), The Cell Factory presents pre-clinical results on the new products of the 2nd generation EV's drugs for treatment of inflammatory diseases

Esperite with its biotech company The Cell Factory has acquired from OPBG the full rights to the IP and the international patent family covering the invention and the therapeutic use of the EV's products. In collaboration with Women's and Children's Health Department of the University of Padua, Italy they are presenting the new generation EV's biologic drugs bio-activated with Annexin V targeting multiple inflammatory diseases i.e.: Crohn's disease, drug resistance epilepsy, stroke. The experimental results will be presented during GISM congress in Assisi, Italy in April and ISEV meeting in Barcelona, Spain in May 2018.

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Esperite's biotechnology company The Cell Factory in collaboration with Women's and Children's Health Department of the University of Padua have developed the 2nd generation of clinical grade extracellular vesicles (EV's) enhanced with the protein Annexin V (EV-AnV). We have demonstrated that Annexin V significantly improves the anti-inflammatory and anti-immunogenic properties of the clinical grade EV's in different experimental models in vitro and in vivo.

The anti-inflammatory properties of EV-AnV's have been initially discovered by the research team led by Prof. Muraca and Dr. Fierabracci at Bambino Gesù Children's Hospital, Rome, Italy. Esperite has acquired from OPBG the full rights to the IP and the international patent

family covering the invention and the therapeutic use of the EV's products. The new technology of the 2nd generation AnV-EV's drugs is protected by the patents already granted in Europe and China.

Annexin V is the protein naturally occurring in humans. It plays important role in wound healing process, blood coagulation, and programmed cell death. Annexin V can bind to negatively charged phospholipids i.e. phosphatidylserine on the surface of apoptotic bodies. Muraca and Fierabracci team has found that Annexin V gain new properties when binds to EV's. The AnV-EV's complex has very strong anti-inflammatory and immunosuppressive properties exceeding the naive EV's and MSCs anti-inflammatory activity and using different mode of action.

In recent studies, The Cell Factory and the University of Padua have tested the anti-inflammatory properties of AnV-EV's in different in vitro and in vivo models. The experiments were performed using clinical grade EVs manufactured by The Cell Factory. The EV's were bound to the Annexin V (AnV-EV's) and tested in an in vitro assay of a mixed lymphocyte reaction with splenocytes from two mice strains (C57BL/6 and BALB/c). AnV-EV's exhibited a suppressive effect on activated B and T lymphocytes in a dose responsive manner. The inhibitory effect was significantly higher with AnV-EV's when comparing to naïve (unmodified) EV's. These results are in line with previously observed anti-inflammatory activities of MSC-derived EV's and indicate an easy and reproducible methods of enhancing the natural properties of EV's. In addition, for the first time the AnV-EV's activity has been tested in in vivo animal models. AnV-EV's were injected via enema in the in vivo mice model of dextran sulfate sodium (DSS)-induced colitis. The results demonstrated dramatic improvement of both clinical and morphometric/histological scores (body wt, disease activity index, colon length and histological parameters) when comparing to naïve EV administration via enema. Free (unbound) AnV administration had no effect on colitis severity. The experiments show that EV's and AnV-EV's induced a different pattern of cytokine expression in colon mucosa what indicates different mechanism of actions of the naïve EV's and the 2nd generation AnV-EV's product.

The results of the experiments demonstrating activity of the 2nd generation AnV-EV's drug candidates will be presented during the Gruppo Italiano Staminali Mesenchimali (GISM) congress in Assisi, Italy 12-13 April 2018 and at the poster sessions and during the lectures at the International Society for Extracellular Vesicles (ISEV) meeting in Barcelona, Spain 2-6 May 2018.

The clinical grade EV's were used in testing of the activity of the AnV-EV's. The Cell Factory is leading the EV's field manufacturing the ultra-pure vesicles according to the GMP guidelines. The Cell Factory has developed a proprietary production process of MSCs and MSC-derived EV's using only fully defined raw materials (ancillary products) during entire production process. MSCs and EV's are manufactured without animal derived components, and human derived undefined components i.e. serum, undefined serum replacements, plasma, platelet lysates, gelatine etc. The Cell Factory technology eliminates the risk of product contamination with pathogens, unknown active substances and external EV's. The Cell Factory production process significantly improves the EV's purity, quality and batch-to-batch reproducibility. Esperite controls the entire production process starting from

procurement of the source material (via bio-bank), donor selection, international transport of the biological products (controlled cold-chain), tissue processing, storage (cryopreservation in liquid nitrogen), cell extraction and expansion, EV bio-production and purification, final product preparation and release. Production process is designed and validated according to GLP/GMP standards and follows the international guidelines dedicated for production and clinical use of biological medicinal products. Stem cells expansion is performed in the most efficient culture systems using 3D microcarrier beads and scalable stirring bioreactor systems. In addition, the closed system can be fully automated and the entire production process (including downstream concentration and filling) can be performed in a lower sterility grade lab environment. The Cell Factory's proprietary closed cell culture system and multi-harvest EV's batch production provide new standards in biologic drugs production and resulting in significant cost reductions without compromising product quality. Ultimately, EV's can be produced at lease 10-times more efficiently and cheaper when comparing to allogenic MSCs equivalent.

In addition to the EV's production system The Cell Factory has developed the new method for EV's quantification available for the scientific and biotech community. It is worth stressing that most of the studies are using EV's produced in undefined culture media containing serum or platelet lysate often contaminated with unknown nanoparticles and extracellular vesicles of human or animal origin. Current quantification methods do not allow precise enumeration of EV's and therefore it is very difficult to compare the experimental results coming from different groups. EV's quantification is currently one of the biggest challenges in the EV's field. Lack of standardized analytical instruments and methods for the EV's quantification have significant impact on the quality and reproducibility of scientific data and clinical translation of the EV's drug candidates. Unfortunately, there is no single instrument or analytical method which could quantify EV's and recognize the EV's from non-EV's particles.

Most published papers rely on protein measurement for EV quantification, or the nanoparticles quantification. EV's quantification using protein content has been recognized as highly inaccurate and influenced by the isolation procedure and culture conditions. Nanoparticles quantification systems i.e. NTA, DLS, TRPS cannot recognize between the EV's and the contamination particles of a similar size. As a consequence, inaccurate quantification of EV's is jeopardizing comparison of results from different laboratories and delays a drug development process. The Cell Factory has developed and validated new method for EV's quantification using a combination of 3 techniques: nanoparticle tracking (NTA), multiparametric immunophenotyping (FACS) and immunomagnetic cell sorting adopted to EV's particles (MACS). Using our method different EV's can be precisely quantified based on different markers combination e.g. tetraspanin proteins (CD9, CD63, CD81). This method is not limited however to the tetraspanins and other markers can be used for detection and quantification of EV's. The method will be presented during the congresses in 2018 and will be published in the peer-review journal soon. We hope that using our quantification method the EV's field will develop faster and bring more quality EV's drug products into the clinic.

The Cell Factory is currently developing EV's biologic drugs for:

- CF-MEV-107 for Crohn's disease (drug-resistant perianal fistulae)

The Cell Factory is leading a translational project on EV's first in man use in treatment of Crohn's disease perianal fistulas. Inflammatory bowel disease (IBD) encompasses a spectrum of diseases affecting 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 normal activity and may lead to complications such an increased risk of cancer and life-threating systemic inflammation.

Epidemiology and market estimation: IBD affects approximately 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-117 for Epilepsy (acute and chronic drug-resistant epilepsy)

The Cell Factory is developing MSC-EV's drug candidate 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 estimation: 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 exceed 15 billion USD in the United States alone.

- CF-MEV-126 for stroke (brain stroke and acute injuries of central nervous system)

Brain stroke is the most devastating neurological disease with no effective therapy available yet. The brain damage could be significantly reduced if anti-inflammatory and neuroprotecting treatment is applies immediately after stroke or injury. Esperite is looking for partners to support the development of extracellular vesicle therapeutics.

Epidemiology and market estimation: According to WHO, 1 in 6 people will have a stroke during lifetime and 6 million people die because of stroke every year. Those who survive, very often suffer from severe physical and cognitive impairments due to brain damage following stroke. CDC estimates the brain stroke related costs on 34 billion USD every year only in the United States.

About the partners:

The department of Woman's and Child's Heath of the University of Padua is tertiary paediatric academic care centre, serving the entire North East region of Italy, devoted to provide excellence in patient's care, teaching and research, also including a ten-store research building. It is one of the eleven fully recognised Italian Children's Hospitals.

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

The Cell Factory is a company of ESPERITE Group, focused on innovative drug products development, clinical translation and commercialization using autologous mesenchymal stromal cells (MSCs) and allogenic MSC-derived extracellular vesicles (MSC-EV's). TCF-Biotech goal is a development of the highest quality therapeutic tools for affordable treatment of unmet medical needs.

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 website at www.esperite.com