

Short Commentary

# Immortalomunea TM: Advnaced lentivirus transduced biocomplexes for the generation of semi-autologous immortalized cell line vaccines for cancerous diseases and HIV infections

\*John Ioannis Grigoriadis

Biogenea Pharmaceuticals Ltd, Greece.

\*Correspondence to: John Ioannis Grigoriadis, Biogenea Pharmaceuticals Ltd, Greece.

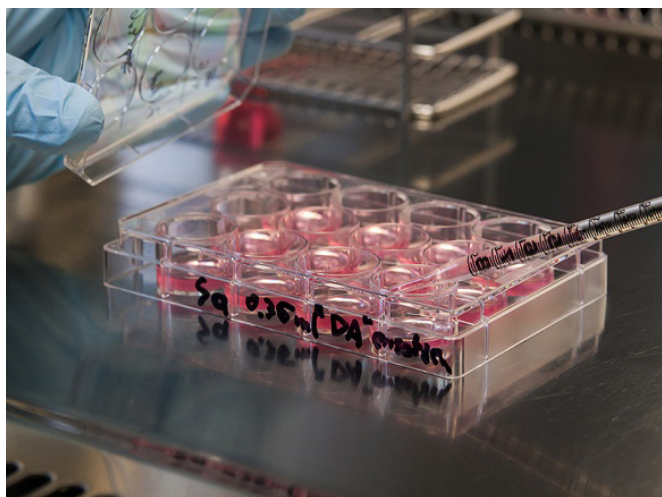
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Dendritic cells are the professional antigen presenting cells of innate immunity and key players in maintaining the balance of immune responses. Studies with dendritic cells are mainly limited by their low numbers in vivo and their difficult maintenance in vitro. Dendritic cells are the professional antigen presenting cells of innate immunity and key players in maintaining the balance of immune responses. Studies with dendritic cells are mainly limited by their low numbers in vivo and their difficult maintenance in vitro. In summary, in “biogenea pharmaceuticals ltd” we successfully generated several immune T and dendritic cell line living vaccines using conditional immortalization where the generated dendritic cell lines demonstrate the characteristic immunophenotype of primary dendritic cells to facilitate further studies on immunomodulatory properties of dendritic cells.

Allogeneic human immature dendritic cell lines derived from a class I & II HLA3-A3-B44 CD34+ progenitor cell.

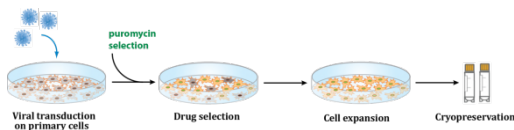


Numerous clinical trials have demonstrated the safety of dendritic cells vaccines, and more than 1000 patients have received dendritic cell vaccines with no serious adverse events associated with the therapy and clinical responses in one half of patients The CA19-9, CA125, DU-PAN-2, and B72.3 antigens have been shown to be expressed in many human pancreatic cancer cells, and C01 7-1A and B72.3 have being used for immunotherapy. Here, in Biogenea Pharmaceuticals Ltd we provide a method of enhancing immunity by modifying a dendritic cell (DC) in vivo or ex vivo to produce an immature immortalized dendritic cell line enhancing immunity in pancreatic cancer patients. OurGenea-Pancretovimortal24585 composition is a pancreatic cancer patient derived tumor lysate pulsed with a immortalized cell line mixture dedicated to the treatment of pancreatic cancer by the use of lentivirus of the CEA, Muc-1, TRICOM, CO1 7-1 A, OC 125 and B72.3, DU-PAN-2 antigen transfected immature transduced dendritic cell lines as an advanced semi-autologous living (DC)-vaccine. Genea-Cordimmortalun24874: Immortalized Human Cord Blood-Derived Stem Cells for the generation of conditionally immortalized universal progenitor cell lines with multiple lineage potential and Immunosuppressive Characteristics.



## Genea-Pancretovimortal24585

A Mixture of two allogeneic human pancreatic derived immature dendritic cancerous immortalized cell lines stably transduced with a retroviral vector for the endogenous encoding of the CEA, Muc-1, TRICOM, CO1 7-1 A, OC 125 and B72.3, DU-PAN-2 respectively on



Cell banking of mesenchymal stem cells (SCs) from various human tissues has significantly increased the feasibility of SC-based therapies. Sources such as adipose tissue and amnion offer outstanding possibilities for allogeneic transplantation due to their high differentiation potential and their ability to modulate immune reaction. Limitations, however, concern the reduced replicative potential as a result of progressive telomere erosion, which hampers scaleable production and long-term analysis of these cells. In Biogenea Pharmaceuticals Ltd for the first time we incorporated methods for preparing multi-potential immortalized stem cells having a pre-selected expression of MHC antigens. Our Genea-Cell lines consisting of two human cord blood-derived immortalized somatic stem cell lines generate by ectopic expression of the catalytic subunit of human telomerase (hTERT). hTERT overexpression resulted in continuously growing SC lines that were largely unaltered concerning surface marker profile, morphology, karyotype, and immunosuppressive capacity with similar or enhanced differentiation potential for up to 87 population doublings. can be Our universal stem cell lines can be used to generate histocompatible tissues/organs for transplantation. The process comprises the use of targeting vectors capable of gene knockout, insertion of site-specific recombination cassettes, and the replacement of histocompatibility alleles in the stem cell. We incorporated novel knockout vectors which are used to delete designated HLA-B44, HLA-B7, HLA-B8, HLA-B35, HLA-B52, HLA-B60, HLA-B39, and HLA-B48 HLA-DR7, HLA-DR4, HLA-DR13, HLA-DR15, HLA-DR3, HLA-DR1, HLA-DR11, HLA-DR8, HLA-DR9, HLA-DR12, HLA-DR14 and HLA-DRBL, HLA-A allele selected from the group consisting of HLA-A2, HLA-A1, HLA-A3, HLA-A24, HLA-A29, and HLA-A33 regions of one chromosome. Recombination cassette vectors were used to delete the same region on the second chromosome and deposit a site-specific recombination cassette which can be utilized by replacement vectors for inserting the new MHC genes on the chromosome of the engineered cell. Our advanced methodology pertains to cells, tissues, for the generation of conditionally immortalized progenitor cell lines with multiple lineage potential

### Genea-Cellgeneroglimmortal737

A Combinations of Transgenes in LV for Reprogramming Immune Precursors into two Antigen-Loaded immortalized Dendritic Cell lines for the DC-endogenous expression of the cALLa/NEP, ABCC3, GPNMB, NNMT, and SEC61γ transduced antigens on immortalized class I & II HLA3-A3B-44-Dendritic Cells lines (iDC) for T Cell Expansion after Stem Cell Transplantation.

Malignant brain tumors carry a poor prognosis even in the midst of surgical, radio-, and chemotherapy. With the poor prognosis of brain tumors the available therapeutic treatments, there exists a significant need for more effective therapies to treat such tumors. Our Genea-Cellgeneroglimmortal737 is based, on the discovery that vaccines



based on cancer stem cell antigens are exceptionally useful for therapy of cancer. Immunization of patients with endogenous expressed of the cALLa/NEP, ABCC3, GPNMB, NNMT, and SEC61γ transduced dendritic cell lines pulsed with autologous tumor lysate from isolated cancer circulated stem cells provided a significant survival benefit as compared to immunization with dendrit The principle of this approach is to educate immortalized immature antigen-presenting cells, such as dendritic cells, to recognize tumor antigens by fusing them on pulsed differentiated tumor cells. Cancer stem cells were found to express major histocompatibility (MHC), indicating that they can display antigens. Our advanced cell fusions can be useful in providing antigenic compositions for treatment of cancers (e.g., neural cancers such as gliomas).

### Genea-Hivotranceral437856

A cord blood derived Non-Transformed, transduced, Immortalized Human double negative il-2 depended T-tropic lymphocyte cell-line for the expression of the CD4D1D2CAR and HTLV-1 p30II oncoprotein.



Genea-Hivotranceral437856 advanced medicinal services include a composition comprising a cord blood derived Non-Transformed, transduced, non-transformed, immortalized T-lymphocyte cell-line, wherein the T lymphocytes are IL-2 dependent and interact

with an extracellular matrix and supports productive infection and replication by T-tropic HIV. Our T-lymphocyte cell-line cells are polyclonal. In another aspect, the T-lymphocyte cell-line are infected with a lentivirus that expressed THE CD4D1D2CAR and an HTLV-1 p30II oncoprotein. Our Genea-Hivotranceral437856 T cell line composition endogenously express the chimeric antigen receptor of CD4 extracellular, transmembrane domains and a CD3 zeta signaling domain where the CD4 extracellular domain binds gpl20 expressed on the surface of cells infected with HIV.

Biogenea Pharmaceuticals<sup>TM</sup> is the first Inter-Balkan Pharmaceutical Biotechnology Company since leading the way since 2005 in Red Biotechnology applications, in Cryobiology and in Autologous Cellular Therapy of Degenerative Diseases (cardiological diseases, neurological conditions and metabolic disorders).

### **Biogenea Pharmaceuticals focuses**

- on the collection, processing, cryopreservation and cGMP (according to Good Manufacturing Practice) production -for solely autologous use - of cellular therapeutical solutions from blood (bone marrow, peripheral blood, cord blood) or blood compounds for human use.
- in collaboration with Regenotech on stem cell expansion technologies, which were created in the research laboratories of NASA (National Aeronautics and Space Administration).
- on the cGMP production of advanced medicinal products (1394/2007/EC) for solely autologous use from skin, dental pulp, cord tissue). (In preclinical-research phase: 2008-2009).
- on certified genetic analyses in collaboration with International Referral Centers.
- on copyright protection according to the American and/or European Copyright Agency
- Preventive Cryopreservation Insurance of Primordial Cells & Therapeutic Applications.
- Continuous update and prompt training of interested Donors and Clinicians of Public and Private Health Centers and Hospitals, about the progenitor cells applications.
- Immediate availability of the stored samples 365 days a year, 7 days a week, 24 hours a day.
- Complete attunement with the specifications set by the European Accreditation Organization for cellular therapy (FACT/JACIE/NETCORD), the American Association of Blood Banks (AABB) and the relevant Greek Presidential Decretal 2004/23 for the tissue/cell banks, with the use of cGMP methods.
- Control of Plasticity of progenitor cells based on the detailed Validation Master Plan of the Standard Operating Procedures (SOPs) regarding their hematopoietic origin (Methocult).
- Fully Automated Viability Control of the cryopreserved progenitor cells with automatic luminometric device, which increases the reproducibility and the accuracy of the results in contrast to the common laboratory techniques for detecting dead cells microscopically (Trypan Blue staining).
- Validated Molecular Diagnostics service provision (detection of HIV1/2, HBV, HCV, CMV, Syphilis, Toxoplasma) applying Real-Time PCR technology (Roche LightCycler).
- Validated ex-vivo cellular and/or tissue expansion of the recently processed cells/tissues, as well as of the cryopreserved cell/tissues in advanced technology Bioreactors, created in the NASA research laboratories, offering unique micro-gravity conditions in alternating electromagnetic field! Cellgenea is the UNIQUE company in Greece able to expand and to use ex-vivo expanded cord blood and adult progenitor cells for therapeutic reasons and clinical trials thanks to the relevant know-how transfer from the research laboratories of NASA and Regenotech Biotechnology Company.
- Storing of progenitor cells in two-chambered bags and cryovials in complete (24 hours a day) controlled and automated liquid nitrogen tanks.
- Continuous control and cross-tracking of the cryopreserved samples with validated LIS-ERP software which ensures the ability to track down and to identify the sample during all the steps of its supply, the processing, the control, the storage and the distribution. The tracking is also used for controlling and identifying all the relevant data about the products and the materials that come in contact with these samples (2004/23/EK).
- Immediate availability and distribution of the sample inside a validated cryotank, in case of therapeutic application.
- Strict security concerning personal data, confidentiality and safety according to the Personal Data Protection Agency.
- Complete bacteriological and serological control of the samples using the automatic analyzers BacT/ALERT and Architect i1000 without any extra rate.
- Life insurance provided to all the members of the different programs of preventive cryopreservation (Cellgenea, Dentogenea, Dermigene, Angiogene, DNAgene, Neurogene, Cardiogene) in cooperation with insurance companies.
- DNA & pharmacogenetic control services for personalized treatment without side effects.