Changing the Face of Modern Medicine: Stem Cell and Gene Therapy

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Abstracts

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Invited Speakers

INV001

General considerations for setting up a clinical trial

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Clinical trials are part of clinical research and at the heart of all medical advances. With the help of clinical trials scientists, physicians and the pharmaceutical industry explore whether a medical strategy, treatment, or device is safe and effective for humans. Because of their importance in the development process of a new drug or treatment, clinical trials must be planned and conducted following national rules and regulations. This provides public assurance that the rights, safety and wellbeing of research participants are protected and that research data collected and reported from these studies are reliable and reproducible. This presentation focuses on key aspects that sponsors and investigators should consider when setting up early phase clinical trials with a cellular gene therapy. It focuses on Good Clinical Practice requirements and other guidance available specific to advanced therapies.

INV002

Quality requirements for GLP tox testing and GCLP clinical testing

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1: GLP SR-TIGET San Raffaele – Telethon Institute for Gene Therapy –GLP Test Facility 2: TCL Tiget Clinical Lab, SR-TIGET 3: SR-TIGET 4: Vita Salute San Raffaele University

The ATMPs are complex biological medicinal products. A safety evaluation of data generated on this product category produced in compliance with the principles of good laboratory practice (GLP) and in a GLP certified test facility has to be conducted before starting human clinical trials and for registration purposes. Being ATMP a complex and very dishomogeneous category of medicine, the non-clinical studies have to be designed on a case by case basis, so that they can provide representative data that address regulatory requirements while assuring scientific integrity and reliability. The quality systems based on GLP and Good Clinical Laboratory Practice (GCLP) principles ensure reproducibility, study reconstruction and data integrity through adequate documentation of study conduct and archiving of data. Laboratories testing human biological samples collected in Good Clinical Practice (GCP) clinical trials are expected to work according to GLP principles. The GCLP guidelines, combining GLP and GCP principles, provide guidance on the quality system to be used when running testing on this sample category. GCLP guidelines may be adopted by regulators during the GCP inspections. Based on the experience of the San Raffaele Telethon Institute for Gene Therapy (SR-Tiget), the key elements of the GLP and GCLP quality systems to be considered (e.g. planning of study, data recording, training of personnel, method validation, etc), challenges and role of Quality Assurance (QA) in setting up a GLP testing facility and a Clinical Lab in the academia environment will be presented.

INV003

Pharmacovigilance in advanced therapy medicinal products (ATMPs): managing greater complexities

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1: ProductLife Group

In its website EMA states: ''All relevant legislation and guidelines regarding pharmacovigilance in the European Union (EU) are applicable to advanced therapy medicinal products (ATMPs).'' ATMPs, however, present peculiar challenges and require different approaches to traditional products not only in their pharmaceutical and clinical development, but also in the management and follow-up of post-approval activities. These drugs are defined in EC Regulation 1394/2007 as ''complex products'', which is reflected in the overall product lifecycle. As such, EMA recently released a draft revised guideline on safety and efficacy follow-up and risk management of ATMPs. Once the revision period is completed, the document will replace the current 10-year-old guideline. This presentation will focus on the main similarities and differences between ATMPs and traditional products, with a particular focus on the need for: 1- a risk-based approach 2- timely interactions with EMA to detect (and mitigate) risks 3- long-term follow up of seriously ill patient population where Adverse Events are frequent 4- post-approval studies. A few real-life examples will be shared during the presentation.

INV004

Registry platform for gene and cell therapy: the EBMT approach

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No abstract available

P159

Immunoexpression of PSD95 and synaptophysin in the motononeurons of the lumbosacral spinal segments of mouse during experimental hypogravity

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The study of the adaptive and compensatory reorganisation of motor system in condition of weightlessness is a critical problem of space biology. In this work we investigated the level of functional activity of motoneurons in the lumbosacral spinal cord of the mouse after simulating of hypogravity on the model of antiorthostatic hanging of the hindlimb. The experiments were performed on 10 mature male mice of c57black/6 line with weight 28 ± 8g. The level of functional activity of spinal neurons was evaluated based on degree of expression of the marker proteins: synaptophysin on the presynaptic membrane and the PSD95 on the postsynaptic membrane. The analysis of the immunohistochemical reaction against these two marker proteins demonstrated a decrease in the level of immune expression of both proteins in motoneuronal bodies in the experimental animals after 30 days of antiorthostatic hanging. At the same time, the immune expression of PSD95 was decreased more significantly compare to immune expression of synaptophysin (decreased by 36% vs. by 25%) from the level of immune expression of these proteins in the mice of the control group. Thus, these results support that the development of the motor dysfunctions during hypogravity can be associated with changes in the motoneurons of the lumbar spinal cord. This work was funded by the subsidy allocated to Kazan Federal University for the state assignment in the sphere of scientific activities, No 17.9783.2017/8.9.

P160

Decellularized extracellular matrix of human mesenchymal stromal cells as a novel biomaterial for regenerative medicine

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Multiple bioactive products secreted by stem and progenitor cells, in particular extracellular matrix (ECM) proteins, are actively involved in the modulation of tissue repair and regeneration. Mesenchymal stromal cells (MSC), a promising source of multipotent adult stem and progenitor cells for cell therapy and tissue engineering, produce a wide range of bioactive molecules including ECM components thus regulating the regeneration processes. The aim of our study was to develop a novel biomaterial based on decellularized ECM produced by human MSC cultured in cell sheets. Several agents for decellularization were selected based on the conservation of ECM structure and effectiveness of DNA removal: CHAPS, sodium deoxycholate, DNAse I and apoptosis inductor (rotenone). Optimal protocols for decellularization of ECM produced by MSC (immortalized human MSC, ATCC) cell sheets were developed. It was shown by different methods that the structure of obtained biomaterial was meshy and branched. Structural ECM proteins (collagen I type, fibronectin and laminin) were preserved after decellularization. The viability and proliferation of MSC and human umbilical vein endothelial cells (HUVEC) cultured on decellularized biomaterial were retained, and cells aligned the biomaterial and remodeled it. CFU test showed that MSC formed denser colonies on decellularized biomaterial compared to plastic. Our results demonstrate the biological activity of ECM components produced by MSC and provide the basis for developing biomedical cell-free products for regenerative medicine. The study was funded by the Russian Ministry of Education and Science grant #MK-2422.2017.7 and conducted using biomaterial collected under RSF grant #14-50-00029.

P161

How to find the right dose for successful transition of ATMPs from the nonclinical to the clinical development stage

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1: Biopharma Excellence

Transition from nonclinical to clinical stage is an important step in drug development. Finding the right dose for the first in human study can be a challenging undertaking for biopharmaceuticals. For Advanced Therapy Medicinal Products (ATMPs) this is even more challenging, as candidates of this product category rarely follow common principles such absorption, distribution, metabolization and excretion. Moreover, a classical dose-response relationship does not apply. For example, cell-based products can proliferate, differentiate and even persist lifelong in a different phenotype than initially administered. Furthermore, virus-based ATMPs such as oncolytic viruses can replicate in target tissues. With this even Paracelsus' toxicology principle ''only the dose makes the poison'' is in question, which was applicable for more than five centuries. As the ''acting dose'' can be very different from the administered dose the dose finding exercise for ATMPs is often about finding answers to the question: How to dose a living drug? Based on real-life case studies, this contribution will address how dosing approaches can be established and which key questions need to be answered for a tailored dose-finding exercise.

P163

Assessment of bystander effects of mesenchymal stem cells carrying a cytosine deaminase suicide gene on glioma cells

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1: Ajou university

Glioblastoma multiform (GBM) is the most severe cancer in the nervous system. Despite the progress has been made in treating GBM, the most effective therapy including combination of chemotherapy and radiotherapy has remained as a palliative cure. Recently, stem cells carrying suicide gene have emerged as the therapeutic candidates for the bystander effects on