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Summary report on the EMA workshop on stem cell-based therapies

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7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom

Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8545

E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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Table of Content

1. Introduction	3
2. Agenda	4
3. Keynote lectures.....	6
4. Panel discussions	14
5. Conclusions	22

1. Introduction

The European Medicines Agency (EMA) assembled for the first time European and international experts from academia, regulatory authorities (Europe, Japan, United States and others) and pharmaceutical industry, in a workshop on 10 May 2010, to review opportunities and difficulties in developing stem cell-based therapies and to discuss regulatory challenges.

“Today’s discussion will pave the way for the first European marketing authorisation application for a stem cell-based product” said Thomas Lönngren, Executive Director of the EMA.

Research into stem cell-based therapies has increased dramatically over the past few years with ongoing clinical studies in adult stem cells and exploration of embryonic stem cells and induced pluripotent stem cells (artificially reprogrammed adult cells) for possible future clinical applications. “Stem cells hold the promise of an unlimited source of cells for therapeutic applications to treat patients who have no or only unsatisfactory treatment options. However, these therapies bear certain risks, such as tumourigenicity and immunorejection, and hence need to be carefully regulated with the input from multi-disciplinary expertise”, said Christian Schneider, chair of the CAT.

Within the European Union, some 40 clinical trials are currently exploring the use of stem cells in regeneration of lost or damaged tissue (heart, skin, bone, spinal cord, liver, pancreas and cornea) and in haematological or solid-organ malignancies. The majority of these trials are using mesenchymal cells derived from adipose tissue, bone marrow, stromal cells and connective tissue. A small proportion of the trials are using haematopoietic stem cells. The Agency has been informed about the intent of a European manufacturer to submit the first application for marketing authorisation for a stem cell-based product.

The Agency’s committees have been advising pharmaceutical companies on stem-cell research at different stages of development for several years. The CAT has confirmed classification as ‘advanced therapy medicinal products’ (ATMPs) of three different stem-cell therapies. The Scientific Advice Working Party, in conjunction with the CAT, has given scientific advice on the quality, preclinical and clinical development of seven stem-cell products. The CAT is currently evaluating, within certification procedures, quality and non-clinical data for stem-cell ATMPs under development by European small and medium-sized enterprises.

Importantly, the workshop was part of the public consultation process on the first dedicated regulatory guidance document on stem-cell research and development. The draft reflection paper builds upon the experience gained so far through extensive dialogue with European experts and pharmaceutical industry and was developed by the Agency’s Committee for Advanced Therapies (CAT), together with the Cell-based Products Working Party and Biologics Working Party.

The present report contains information on the topics, speakers and discussions, which took place at the workshop on 10 May 2010.

2. Agenda

The workshop on stem cell-based therapies was composed of 2 sections, a morning section with scientific and regulatory keynote lectures and an afternoon session with Panel discussions on relevant sections of the reflecting paper on stem cell-based products. The EMA Executive Director Thomas Lönngren opened the workshop with some words on the EMA initiatives and prospects in the area of cell therapy. He highlighted the Agency's activities in particular on stem cell-based therapies as well as the clinical experience in this area in the EU. CAT Chair Christian Schneider and CAT Vice chair Paula Salmikangas invited participants to exchange their experience and views on the scientific and regulatory requirements of stem cell-based products. The chairs further emphasized the role of the Committee of Advanced Therapies to guide sponsors in the development of Advanced Therapy Medicinal Products.

The details of the agenda can be found below:

Morning session - Lectures

(Topic – Speaker)

Opening words Mr Thomas Lönngren, Executive Director EMA

Welcome Dr Christian Schneider / Dr Paula Salmikangas

EU support to stem cell research Dr Charles Kessler, EC DG Research

Keynote Lectures

Human embryonic stem cells: Consideration for therapeutic development Dr Jane S. Lebkowski, Geron Corporation

Induced pluripotent stem cells Prof Marc Peschanski, I-stem, Evry, France

Mesenchymal stem cells: Science and therapeutic applications Dr Dirk Buscher, Grifols

Haematopoietic stem cells Dr Neil Rodrigues, NIH Center for Biomedical Research Excellence in Stem Cells at Boston University, USA

Neural stem cells Prof Gianvito Martino, Division of Neuroscience San Raffaele Hospital, Milan, Italy

Regulatory Notes

Stem cell-based medicinal products as ATMPs in the EU / Introduction of EMA reflection paper Dr Paula Salmikangas / Dr Tiina Palomäki (CPWP member, Rapporteur)

Overview of Regulation of Stem Cell-based products by the USA FDA Dr Kimberly Benton, Division of Cellular and Gene Therapies, Office for Cellular, Tissue and Gene Therapy, CBER, FDA

Afternoon session – Panel discussions

(Topic – Speaker)

Topic 1. Quality criteria and starting material (55 min) Chair: Dr M. Menezes-Ferreira

Prof Jean-Hugues Trouvin (BWP Chair, CAT)

Dr Lyn Healy (UK stem cell bank, NIBSC)

Dr María Pascual (Cellerix)

Dr Paula Salmikangas (CPWP, CAT)

Dr Stephen Minger (Cell Technologies, GE Healthcare)

Topic 2. Animal Models (30 min) Chair: Dr Carla Herberts (CPWP)

Dr Hans Ovelgönne (CAT, SAWP)

Prof Beatriz Silva Lima (CAT, CHMP, SWP)

Prof Balázs Sarkadi (CAT)

Dr Tiina Palomäki (CPWP)

Prof Jürgen Hescheler (Universität Köln, DE)

Topic 3. Biodistribution and Niche (30 min) Chair: Prof Asterios Tsiftoglou (CAT, CPWP)

Dr Egbert Flory (CAT, CPWP)

Prof Kathryn Wood (University of Oxford, UK)

Dr Denis Corbeil (Technische Universität Dresden, DE)

Dr Ross Hawkins (NIBSC)

Topic 4. Tumorigenicity(30 min) Chair: Dr Egbert Flory (CAT, CPWP)

Prof Toivo Maimets (CAT)

Dr Jane S. Lebkowski (Geron Corporation)

Dr Sophie Lucas (CAT, CPWP)

Dr Heidrun Holland (Universität Leipzig, DE)

Dr Arnaud Foussat (TxCell)

Topic 5. Clinical aspects (55 min) Chair: Prof Giovanni Migliaccio (CAT, CPWP)

Prof Andreas Zeiher (J.W. Goethe University Frankfurt, DE)

Prof Paolo De Coppi (UCL, London, UK)

Dr Gopalan Narayanan, (CAT, GTWP)

Dr Romaldas Mačiulaitis, (CAT, CHMP, CPWP, PDCO)

Ms Elona Baum (CIRM)

Closing remarks Chairs

3. Keynote lectures

Keynote lectures and regulatory notes were intended to give an overview of the current state of the art knowledge within each group of stem cells as well as to illustrate regulatory requirements, both in EU and USA. In addition, incentives and funding opportunities available in the EU for the development of stem cell-based therapies were presented.

A short biography and abstract introduces the speakers and contents of the scientific and regulatory keynote lectures.

3.1. *EU support to stem cell research*

Charles Kessler, PhD

Biography. Charles Kessler is Principal Scientific Officer at DG Research at the European Commission. He works in the Health Biotechnology Unit of the Health Directorate of the Research Directorate-General and coordinates work on New Therapies such as Cell and Gene Therapy, Tissue Engineering and Immunotherapy.

Abstract. EU support to stem cell research is available through the 7th framework programme, which aims at improving the health of European citizens and increasing competitiveness of European health-related industries and businesses. The 7th framework programme funds basic and applied research which includes translational research and early clinical trials. A budget of about 6.1 billion € is available to multidisciplinary networks for a funding period of 7 years. The transition to in-patient trial stage has been identified as the bottle neck; hence the EC is focusing the attention in trying to support this stage of development. EU stem cell research is related to the areas of banking, cell and gene therapy, cancer research, exploration of underlying basic mechanisms and regenerative medicines. Human embryonic stem cell research can be funded by EU programmes on the basis of scientific and ethical reviews and where national laws are respected. The following EU countries are currently engaged in human embryonic stem cell research: Sweden, United Kingdom, Finland, Belgium, Spain, France, Czech Republic, the Netherlands and France. With the Regenerative medicine calls 1, 2 and 3, the European Commission is currently supporting a total of 17 projects in the area of cell culture and production, biotherapeutics, implants and tissue engineering and development of instruments and vectors. Future opportunities for funding will likely focus on clinical trials and encourage submission and engagement with regulators and SMEs.

3.2. *Human Embryonic Stem Cells: Considerations for Therapeutic Product Development*

Jane S. Lebkowski, PhD

Biography. Jane Lebkowski joined Geron Corporation in 1998 and is currently Senior Vice President and Chief Scientific Officer of the Regenerative Medicine Division. Dr. Lebkowski heads Geron's human embryonic stem cell program, and is responsible for all research, preclinical development, product development, manufacturing, and clinical development activities. Prior to Geron, Dr. Lebkowski was Vice President of Research and Development at Applied Immune Sciences. Following the acquisition of Applied Immune Sciences by Rhone Poulenc Rorer (RPR, currently Sanofi-Aventis), Dr. Lebkowski remained at RPR as Vice President of Discovery Research. During Dr. Lebkowski's tenure at RPR, she coordinated preclinical investigations of gene therapy approaches for treatment of cancer,

cardiovascular disease and nervous system disorders, and directed vector formulations and delivery development. Dr. Lebkowski received her Ph.D. in Biochemistry from Princeton University in 1982, and completed a postdoctoral fellowship at the Department of Genetics, Stanford University in 1986.

Dr Lebkowski has published over 70 peer reviewed papers and has 12 issued U.S. patents. Dr. Lebkowski serves as the co-chair of the Industrial Committee of the International Society for Stem Cell Research and serves on the editorial boards of several scientific publications.

Abstract. Human embryonic stem cells (hESCs) are a promising starting material for the production of human cellular therapeutics as they have an indefinite proliferative lifespan in culture enabling production of large, well-characterized, master and working cell banks for the cGMP manufacture of the cell therapy for its entire product life cycle. In addition, hESCs are pluripotent and hence can be differentiated into essentially all the cell types of the body. Production of hESC-based therapeutics typically involves 1) thawing an aliquot of hESCs from a master or working cell bank; 2) expanding the hESCs to a desired cell number; 3) differentiating the hESCs to the desired mature cellular composition and 4) harvesting the final product for release testing and formulation for use. There are numerous critical technologies that need to be developed for the production and testing of each hESC-based therapeutic ranging from cell expansion and differentiation protocols, cellular composition analysis, and preclinical safety and efficacy assessments. In addition, there are numerous considerations that must be assessed when developing a hESC-based therapeutic. Many of these questions are common to all stem cell based therapies. These considerations include: 1) the quality, characteristics, and adventitious agent status of the hESC line chosen as the starting material; 2) the details and control of the production process used to produce the final cellular therapeutic; 3) the methodology used to test the composition and function of the final product; 4) the exact modality in which the cellular therapeutic will be administered and used in the clinic; 5) the models to test the efficacy, safety and mode of action of the hESC-based therapy; 6) the cell doses required for therapeutic benefit; 7) the distribution of the cells once administered; 8) possible toxicological effects associated with the presence of the cells in vivo; 9) any tumor or ectopic tissue formation produced by the therapeutic cell population; and 10) the design of the clinical protocol to test the safety and efficacy of the therapeutic cell population. Specific, progressive, action plans are required to address these elements throughout the development of the hESC-based therapy.

3.3. Induced Pluripotent Stem Cells, hopes, dreams and nightmares...

Marc Peschanski, PhD

Biography. Marc Peschanski is currently head of the Institute for Stem cell Therapy and Exploration of Monogenic diseases (I-STEM, INSERM/UEVE unit 861, associated to the Association Française contre les Myopathies) in Evry (Paris district).

Hired as a Research Associate at INSERM in 1982, he had obtained previously a MD and a PhD from the University of Paris, the latter on the neurophysiology of pain. He did a post-doctoral training at UC San Francisco. He built his first own team on pain relay neurons in the thalamus, that he analyzed using physiological and anatomical approaches.

From 1985 on, he has changed topics and undertaken in parallel basic research dealing with brain neuroplasticity and pre-clinical studies aiming at using those newly described capacity of adult neurons for therapeutic purposes with fetal neural grafts. In 1991, he moved to the Hospital Henri-Mondor in Créteil to start a translational research INSERM unit that carried out clinical trials of fetal neural grafts (then gene therapy) in patients with Parkinson's and Huntington's disease. Positive results of the latter clinical trial in a disease which has no other known treatment, has led to the organisation of a multi-centre European-wide phase II trial.

Since 2005, he has started a new venture by creating the first and largest Institute for stem cell research in France, I-STEM, dedicated to the exploration of therapeutic potentials of pluripotent stem cells in rare diseases of genetic origin. I-STEM currently comprises more than 85 people in 10 research teams interested in neurological diseases, myopathies, retinopathies and genodermatoses. He has been one of the founders of NECTAR, the Network for European CNS Transplantation And Restoration, and its first chairman (1991-92). He has founded the Clinical Investigation Centre in Créteil in 2001 and coordinated its activity up to 2006. He is currently the chairman of the "STEM-Pole", a network that federates 80 stem cell research teams in the Paris district.

Abstract. Human induced pluripotent stem cells (iPS) have emerged only two and a half years ago, but their application is already envisaged in regenerative medicine. The reason for such a speed lies in the fact that the use of embryonic stem cells (ES) for such an application has already been well discussed, and iPS essentially replicate ES capacities. Producing iPS for regenerative medicine will, however, require adaptation of the original techniques. Potential developments are actively sought on each of the elements of the original reprogramming protocols, concerning in particular the donor cell types, the transcription factor genes and the vectors –with the hope to altogether get rid of any- as well as the culture system and quality controls to be applied. within the framework of the production of clinical grade iPS cell lines.

Quality control (QC) of iPS cell lines is an essential step that requires a coherent demonstration of a series of complementary properties. Once cell lines are produced and controlled at the undifferentiated stage (allowing for amplification and banking), regenerative medicine use requires stem cells to be differentiated up to the specific cell phenotype of interest. This requires protocols that rely on the combination of a series of principles that many years of research on ES cells have largely established. One interesting feature of iPS cell lines is the opportunity that their production offers to provide them with properties of interest through gene engineering. It would be interesting, in particular, to improve reprogramming and differentiation protocols through inserting marker genes, and transcription factors could be introduced in order to push the terminal cell differentiation toward a specific phenotype. The possibility to get rid of transplanted cells that would have turned wild through specific gene engineering is also of major interest. Altogether, the main advantage of iPS is the opportunity that they offer to select genotypes of interest. This may indeed allow the creation of a bank of cell lines with different haplotypes in order to provide for cells compatible with the immune system of any patient in need of a graft. Building such a HaploBank is a most timely task and it is my view that we should create an international consortium on the model of the Human Genome project in order to meet the XXIst century challenge of regenerative medicine.

3.4. Mesenchymal "stem" cells: Science and therapeutic applications

Dirk Büscher, PhD

Biography. Dirk Büscher has a PhD in Biology, from the University of Hannover, Germany. He received his PhD in Immunology, and focused on molecular development biology and stem cell research during his 6 years work at the Salk Institute, La Jolla, California. During his 15 years of academic research, he acquired extensive scientific knowledge, reflected in over 20 high-impact publications.

Dr Büscher worked at Cellerix SA for over 6 years and occupied the position of Vice President of R&D. He obtained an International Executive MBA from the Insituto de Empresa, Madrid, and has recently accepted a position at Grifols SA, Barcelona.

Abstract. Mesenchymal “stem” cells (MSCs) have been described already in the 60s and 70s (Hauner et al., Friedenstein et al.), although the discovery of their potential as stem cells occurred much later in the 90s and early 2000 (Caplan, Zuk et al., respectively). Although mesenchymal stem cells from bone marrow and fat tissue are probably the best characterized and most widely used, several other mesenchymal tissue have been show to contain a multipotent stem cell population. Although the multipotent differentiation for mesenchymal stem cells has been clearly demonstrated in vitro, the in vivo differentiation appears to be more restricted, which may also be linked to fact that most in vivo applications use expanded cell populations.

Within the last years other biological capacities have been described for MSCs that received considerable scientific attention, the secretion of growth factors and cytokines by the MSCs, and their immunosuppressive/immunomodulatory capacity. Thus, paracrine effects elicited by MSCs have been shown in different animal models to improve healing and regenerative processes, induction of neo-vascularisation, ameliorate autoimmune diseases, and/or induce regulatory Tcells. The fact that in most cases MSCs are used in the clinic in a heterologous way and/or as expanded cell population makes them a medicinal product. It also has become clear that production aspects such as isolation technique, type of cell culture media and plates, population doublings, etc will impact the characteristics of the product (MSC population). Nevertheless, there is a consensus within the scientific community on how to define MSCs, and a clear notion exists that surface marker profiles and other characteristics are inherent to MSCs and are not dependent on technical procedures, and thus can serve as identity profile. In contrast the potency of MSCs will be strongly linked to their application and the therapeutic effect desired.

The clinical studies currently ongoing reflect the results and knowledge obtained in academia, and the therapeutic potency of the MSCs is being linked to differentiation or release of paracrine acting factors or immunosuppression/modulation.

3.5. Haematopoietic stem cells

Neil Rodrigues, PhD

Biography. Neil Rodrigues initially studied for a Medicinal Chemistry degree. After he had completed a Masters in Medical Biochemistry, he worked as a research associate in the haematopoietic stem cell laboratory of Professor David Scadden at Harvard Medicial School.

Dr. Rodrigues was then accepted onto a doctoral program at Green College, Oxford University, investigating the transcriptional regulation of haematopoietic stem and progenitor cells and remained at Oxford University to continue post-doctoral training in the laboratory of Professor Tariq Enver.

He recently established his own laboratory at a NIH Center for Biomedical Research Excellence in Stem Cells at Boston University.

Abstract. Haematopoiesis (blood production) is the process by which manifold blood and immune cell lineages are generated from haematopoietic stem and progenitor cells. A rare and relatively quiescent cell type that resides in the bone marrow, haematopoietic stem cells are either fated to self-renew, differentiate, or undergo apoptosis. Progenitor cells, on further differentiation, become progressively restricted to particular types of mature blood cells. Thus, a hierarchy of haematopoietic stem and progenitor cell compartments sustains haematopoiesis throughout the lifetime of an organism. This talk will broadly focus on the intrinsic and extrinsic regulating haematopoiesis at the level of haematopoietic stem and progenitor cells and how these cells become dysregulated in leukaemia. The clinical relevance of haematopoietic stem and progenitor cells in bone marrow transplantation will also be touched on.

3.6. Neural stem cells

Gianvito Martino, MD

Biography. Gianvito Martino received his degree in medicine in 1987 from the University of Pavia, Italy where he stayed to complete his residency in neurology. Soon after, he assumed the position of Visiting Scientist at the Karolinska Institute in Stockholm, Sweden and subsequently moved to the USA to become a Research Associate at the University of Chicago, a position he held from 1991 to 1992. Returning to Italy, he became a Research Associate at the San Raffaele University Hospital in Milan and has been active in research at this hospital ever since. Gianvito Martino is currently Director of the Division of Neuroscience at the San Raffaele University Hospital. He is a member of several scientific advisory boards and has been the President of the Italian Neuroimmunology Society since 2009. He has been recently appointed as honorary professor at the School of Medicine and Dentistry of the Queen Mary University of London, UK. His medical and scientific interests range from the elucidation of the pathogenic mechanisms of to the development of gene and stem-cell based therapies for inflammatory and neurodegenerative CNS disorders.

Abstract. The potential of neural stem/precursor cell (NPC)-based therapies to revolutionize the treatment of neurological disorders is an exciting prospect for modern medicine. The results so far obtained in pre-clinical models of inflammatory as well as degenerative neurological disorders consistently challenge the sole and limited view that NPCs therapeutically work exclusively throughout cell replacement. As a matter of fact, transplantation of NSCs may promote central nervous system (CNS) repair (neuroprotection) through cell replacement but also via bystander capacities, mainly exerted by undifferentiated cells releasing, at the site of tissue damage, a milieu of neurotrophic and immunomodulatory molecules whose release is temporally and spatially orchestrated by environmental needs. These molecules acting in a paracrine fashion are, at least in part, 'constitutively' secreted by stem cells thus representing a sort of stem cell signature. Along with developmental and differentiation plasticity which are cardinal features of NPCs, the concept of therapeutic plasticity – which can be viewed as the capacity of somatic NPCs to adapt their fate and function(s) to specific environmental (e.g. CNS) needs occurring as a result of different pathological conditions – is now emerging. However, still there are some preliminary questions that need to be solved before envisaging any potential human applications of these therapies in neurological disorders. Not only the ideal cell source for transplantation and the best route of cell administration have to be determined, but it is still unclear, and even more challenging, the best way to tightly control the different NPC-mediated mechanism(s) sustaining the repair capabilities of these cells once in vivo transplanted.

3.7. Stem cell-based medicinal products as ATMPs in EU

Paula Salmikangas, PhD

Biography. Dr. Salmikangas is a biochemist by original training, but her main research work career has been in cell and molecular biology of various inherited diseases. Since 2006, she has been an Associate Professor of Biochemistry for the University of Helsinki.

Dr. Salmikangas has worked as a senior researcher at National Agency for Medicines, Finland since 2003. Her main areas of expertise are biological medicinal products, especially cell-based medicinal products and combination products. Dr. Salmikangas has been a member of CPWP since 2005 and a chairperson of CPWP since 2007. She is also a member and vice-chair of the Committee for Advanced Therapies.

Abstract. Five years ago the Cell-based Products Working Party (CPWP) was established under the Committee for Human Medicinal Products (CHMP). At the same time, the European Commission introduced a draft of a new regulation concerning Advanced Therapy Medicinal Products (gene and cell therapy and tissue engineered products). Since 2003, cell and gene therapy products were classified as medicinal products, but tissue engineered products were not regulated at the EU level. The first tasks for the CPWP were assisting the Commission in drafting the technical requirements for cell-based products (dir. 2009/120/EC) and drafting of the first multidisciplinary guidance for both somatic cell therapy and tissue engineered products. Quite soon it became evident that the components in these two product classes can be the same, although the mode of action is different, and thus most of the scientific requirements are same for both groups. Consequently, the concept of cell-based medicinal products was established and the first guideline was adopted in 2006 (CHMP/410869/06), covering general quality, non-clinical and clinical requirements for all cell-based medicinal products. Under the umbrella of the “mother guideline” CPWP, together with CHMP, CAT (Committee for Advanced Therapies) and BWP (biologics working party), has later issued further guidance, including a multidisciplinary guideline on xenogeneic cell-based medicinal products, a reflection paper on chondrocyte containing products for cartilage repair, points for consideration on potency testing for cancer immunotherapy products, and a reflection paper on stem-cell based medicinal products. Depending on the product, the relevant specific guidance should be explored in conjunction with the general, overarching guideline. Where genetically modified cells are used, the available guidance on gene transfer medicinal products should be taken into account (CHMP/GTWP/234523/09, CHMP/GTWP/405681/06). In addition to the above mentioned guidance, the other common guidelines relevant for medicinal products, should be consulted. The GMP guideline and its Annex 2, which is also addressing GMP and manufacturing issues of ATMPs, lay down the basic principles for good manufacturing practices. Furthermore, the relevant ICH (International Conference on Harmonisation) and EMA (European Medicines Agency) guidelines on quality, safety, efficacy and pharmacovigilance issues should be considered, as well as relevant monographs and general chapters of the European Pharmacopoeia. During the past years the cell-based products under development have been facing many limitations and challenges. On the other hand, the risk profiles of different products can vary a lot. These findings led to implementation of a risk-based approach first for cell-based products and now, it has been included also into the legislation (Annex I, part IV, Dir. 2001/83/EC) and applies to all ATMPs. Further guidance is under development to clarify the use of the risk-based approach (CHMP/CPWP/708420/09) as part of the marketing authorisation application.

3.8. EMA Guidance on stem cell-based medicinal products

Tiina Palomäki, PhD

Biography. Dr Tiina Palomäki holds a PhD degree in genetics, and is currently working as a senior researcher at the Finnish medicines agency as a responsible person for preclinical aspects of biotechnological products. She is a member of CPWP and an alternate member of GTWP. Her activities include development of EMA guidelines, and she is the Rapporteur of the current Reflection paper on stem cell-based medicinal products. Prior to joining the Finnish medicines agency she worked 13 years in research, latest as a senior researcher in Biomedicum Helsinki where she was involved in development of human embryonic stem cell –based therapy.

Abstract. As the area of stem cell-based therapies is advancing at increasing pace a need for regulatory guidance is foreseen. Existing EU guidance on cell-based medicinal products (EMA/CHMP/410869/2006) lays down general outlines that are applicable to all cell based medicinal products including stem cells. Stem cells are, however, associated with additional safety concerns which are covered in the current Reflection paper on stem cell based medicinal products. The aim of

the reflection paper is to highlight the potential and theoretical safety concerns based on the current scientific understanding, as well as the technical and methodological challenges related to non-clinical and clinical development of stem cell based products.

The two principal characteristics that define stem cells, i.e. capacity to self-renew and differentiate along multiple lineages make stem cells attractive and promising source for cellular replacement therapies. However, at the same time these same characteristics can be seen as the primary cause of additional risks of tumorigenicity inherent particularly to embryonic stem cells and induced pluripotent cells, as well as of unintended differentiation at ectopic locations.

Stem cells represent a spectrum of different cell-based products with varying amount of scientific data and clinical experience. Similarly, perceived risks associated with different types of stem cells are not the same. Therefore, a risk-based approach for product development and data requirements is recommended.

Scientific knowledge in the field of stem cell biology and advancements in development of stem cell-based therapies are rapidly increasing. Therefore, this reflection paper should be seen as a regulatory reflection of the present stage of scientific knowledge and limited regulatory experience. The regulatory view will evidently evolve along with stem cell science and clinical experience with stem cell based products.

3.9. Overview of Regulation of Stem Cell-Based Products by the U.S. FDA

Kimberly Benton, PhD

Biography. Kimberly Benton received her Ph.D. from the University of Alabama at Birmingham, USA, Department of Microbiology, and performed postdoctoral research at the University of Pittsburgh School of Medicine, Department of Molecular Genetics and Biochemistry before joining the Division of Cellular and Gene Therapies at the Center for Biologics Evaluation and Research, FDA. Her research focused on immune responses to bacterial and viral pathogens. In DCGT, Dr. Benton first served as a Staff Fellow and subsequently became a Chemistry, Manufacturing, and Controls Reviewer of somatic cell therapies. Dr Benton was the Chief of the Cell Therapies Branch prior to her current position as the Deputy Director of the Division of Cellular and Gene Therapies. Her duties focus on oversight of review and regulatory activities and policy development for cellular therapy, gene therapy, xenotransplantation, related products such as therapeutic vaccines and combination products involving cell or gene therapies.

Abstract. Stem cell-based products intended for implantation, transplantation, infusion, or transfer to a human recipient are regulated by the US FDA Center for Biologics Evaluation and Research (CBER) as human cells, tissues, cellular or tissue-based products (HCT/Ps). HCT/Ps are subject to regulation as Biologic Drugs or Devices if they that do not meet all of the following criteria: minimally manipulated; intended for homologous use; not combined with another article; and either does not have a systemic effect or require living cells, or has a systemic effect and is for autologous use, for 1st or 2nd degree related recipients, or for reproductive use (see 21 CFR 1271.10). Most stem cell based products are regulated as Biologics under the existing policies for somatic cell therapy and or gene therapy products. FDA review of clinical studies involving stem cell-based therapies involves evaluation of several factors including: donor eligibility determination; methods for isolating, expanding and maintaining stem cells in culture and/or direct their differentiation into specific cell types; identification of unique properties that allows for design of analytical tests to assess identity, purity, and potency, and management of potential immunological incompatibilities. Monitoring the fate of a stem cell-based product following patient administration such as migration from site of delivery, further differentiation to desired and undesired phenotypes, and functional physiologic integration are

crucial to assessment of safety and therapeutic efficacy. Delivery of stem cells to certain anatomic locations may require novel procedures and/or novel delivery devices. A therapeutic product of cells delivered by certain devices would be considered a Combination Product (see 21 CFR 3.2(e)). The FDA encourages interactions between review staff in the Office of Cellular, Tissue and Gene Therapies and prospective investigators/sponsors to assist in development of applications for clinical testing of investigational stem cell-based products.

4. Panel discussions

The afternoon session of the workshop was organised as interactive Panel discussions on the relevant sections of the reflection paper on stem cell-based products: Quality criteria and starting material, animal models, biodistribution and niche, tumourigenicity and clinical aspects. The following chapter contains a summary of the questions and comments raised by Panelchairs and audience and discussed at the session. Not all questions could be discussed at the session due to time constraints; however, the questions will be discussed and considered in the revision of the Draft reflection paper on stem cell-based medicinal products. The composition and affiliations of Panellists together with a summary of the main conclusion is included. A detailed report on the content discussed is also in preparation, which will be made available to the public at a later stage.

4.1. Topic 1: Quality criteria and starting material

4.1.1. Composition of Panel

Chair: **Dr M. Menezes-Ferreira**

Prof Jean-Hugues Trouvin, Professor of Pharmacy, University Paris Descartes; BWP chair, CAT member

Dr Lyn Healy, Senior Stem Cell Biologist at UK Stem Cell Bank, NIBSC

Dr María Pascual, VP of Regulatory Affairs & Manufacturing, Cellerix

Dr Paula Salmikangas, Associate Professor of Biochemistry, University of Helsinki, CPWP chair, CAT Vice-chair

Dr Stephen Minger, Global Director Research & Development for Cell Technologies at GE Healthcare Cell Technologies

4.1.2. Questions raised & discussed

Panelchair:

Starting Materials –what viral testing and at which stages of development of the selected cell preparation / line?

Relevant markers for assessment of mixed cell populations, phenotypic/genotypic/epigenetic?

“Ideally a combination of markers to be used should be able to distinguish between the different differentiation states of all cell types.”

Purity – consistency of heterogeneity / differentiation

“Attempt to maximize the active moiety in the medicinal product and a reduction and avoidance of cells that do not contribute or negatively impact on the therapeutic activity and safety”

Potency, functional tests and cell markers

“The potency of a stem cell-based product should be measured to define biological activity, number and differentiation status of the cells needed for the intended use”

Tumourigenicity, feasibility for process validation

“During product development / characterisation and validation of the manufacturing process, genotypic stability and phenotypic profile of the intended cell population should be demonstrated for each intermediate.”

Audience:

We have a concern on viral safety of hES or iPS cells which have been established using MEF (mouse embryonic fibroblast cells) as feeder cells. It is known that many rodent cells are contaminated by retroviruses, which possibly transmit to other cells during co-culture. Transmitted retroviruses have an ability to integrate into chromosome of cells. When hES or iPS cells which are contaminated with retrovirus are established, the integrated retroviruses will be hardly detected.

Most of the raw materials/media used for the culturing process are of research grade as of now. How can clinical use be justified?

“Special attention should be paid to the use of growth factors and reagents that may have different impact on different cells in the original cell population.”

We understand the concerns, but it seems to be very difficult to clarify what tests should be required of the sponsors.

Is it required to analyze the degradation profile of the Stem cell product during stability studies? If required what parameter to be considered?

How do we define bio-similar or bio-better in adult stem cell products? If there is a change in donors (for bone marrow derived mesenchymal stem cells) will this be considered a different product?

How should products be handled that are taken from the patient in a surgery room, minimally manipulated in the same room (closed system) and given back to the patient within the same surgical procedure all under the supervision of the same physician. Manufacturing authorisation and full GMP for instance for that case? And the surgery facility?

Given that there is likely to be some uncertainties with the technology, is it relevant that process improvement using “Deming Cycle” continuous improvement methods be applied and, if so, how?

Is it required to mention the passage level in the final Stem cell product label, as the product can be obtained at different passage level?

How to demonstrate the compatibility of the container closure system with the final Stem cell product?

Line 181-182 (of Draft Reflection paper on stem cell-based medicine products (EMA/CAT/571134/2009)). Purity is not always a good thing for stem cell-based medicinal products. For instance, recent evidence suggests that the haematopoietic system is actually maintained by a consortium of HSC subtypes with distinct functional characteristics. See Challen et al., 2010. Cell Stem Cell 6, 265 (5 March 2010) and references therein. This issue should be considered for the “purity” section and rewrite according to the nature of the stem cell-based medicinal product.

Do Lines 133-135 (of Draft Reflection paper on stem cell-based medicine products (EMA/CAT/571134/2009)) imply derivation of new hESC lines under GMP conditions? Wouldn't it suffice to test viral safety etc. in existing cell lines in a comprehensive manner? Different hESC lines show distinct differentiation propensities and it would make little sense investing a lot of time and resources in the derivation of new lines.

Line 172-173 (of Draft Reflection paper on stem cell-based medicine products (EMA/CAT/571134/2009)) it is nearly impossible to have cell identity markers specific for the intended cell population. It is only a particular combination of markers that may be cell-type specific.

4.1.3. Summary of quality panel:

Several aspects were discussed in relation to quality criteria for stem cell-based products including starting material, traceability, viral testing, use of feeder cells, cell characterisation, mechanism of action and means to study and reduce tumourigenicity.

In the case of human embryonic stem cells, the starting material is the initial cell line established from the blastocyst although, according to the Regulators there may be limitations or lack of minimal information on the donors (sperm and egg donors) that should be compensated with more information obtained from testing and characterisation of the starting material. A case-by-case approach on the basis of a risk-assessment and the starting material should be thoroughly characterised before scale-up and banking criteria can be set. The aspects of viral safety of mouse feeder cells with respect to murine retroviruses should be addressed.

The need to identify and qualify suitable markers for phenotypic, genotypic and epigenetic cell characterisation was highlighted. Stakeholders mentioned that several reliable markers are available for undifferentiated stem cells, however, for differentiated cell population markers to characterise for example early cardiac progenitor cell at a later differentiation stage are mostly lacking. Hence, for differentiated cell populations, functionality may be more suitable for the purpose of characterisation.

Panelists and audience exchanged views on the feasibility to characterise the purity of a cell population using positive/negative markers. Finally a combination of marker for identity and purity and functionality was considered to be best suited to characterise a cell combination.

The need for functional assays as potency assays early in development was discussed. There was an agreement that a potency assay is fundamental and should be in place for a phase III study. In general, efforts should be directed to understanding the biological activity of the product and characterising the cell population.

Factors contributing to tumourigenicity need to be understood. However, while studies of karyogenicity (e.g. sequencing) on a quality level are needed, these were regarded as difficult to conduct and to interpret. Hence, it may currently be more reliable to base investigations into the tumourigenicity on both, animal models and quality characteristics, rather than on quality characteristics alone.

4.2. Topic 2: Animal Models

4.2.1. Composition of Panel

Chair: **Dr Carla Herberts** (CPWP)

Dr Hans Ovelgönne, Head of Department, Quality biological medicines at NL institute for health & environment, CAT, SAWP member

Prof Beatriz Silva Lima, Professor at University of Lisboa, Faculty of Pharmacy, SWP chair, CAT, CHMP, SAWP member

Prof Balázs Sarkadi, Head of Department, National Blood Center & Membrane Research Group, Semmelweis University, CAT member

Dr Tiina Palomäki, Senior researcher at Finnish medicines agency, CPWP member

4.2.2. Questions raised & discussed

Panelchair:

Is a homologous animal model necessary for proof of principle studies?

Can safety studies be performed in a homologous animal model and if so, which studies?

When are studies in non-rodent or large animal model necessary?

Audience:

To which extent does *in vitro* evidence for a mechanism of action supporting a “trophic” effect (GF secretion etc.), have to be confirmed *in vivo* and if so, how?

A gold standard for non-clinical data in animal models of neurodegeneration needs to be defined. The precursor/stem cells should be shown to integrate into neuronal brain circuits of the brain in relevant regions. Since cellular events cannot be shown with neuroimaging in patients, unbiased cell counting techniques in 3-D should preferably be used to demonstrate efficacy.

It is not clear whether automatically non-clinical tests using more than one species of animals should be conducted.

The CHMP guidelines require two different species. Is there any advice in the field of cell-based therapies on the need to use immunodeficient animals or larger animals?

For conducting animal models study for European requirements is it enough to conduct only studies in rodents?

Please suggest the availability of animal models for specific diseases such as AMI (Acute Myocardial Infarction), CLI (Critical limb Ischemia), OA (Osteo Arthritis), DCM (Dilated Cardiomyopathy), DM, CS and LC (Specific disease targets).

4.2.3. Summary of animal model panel:

The suitability of various animal model for testing of stem cell-based therapies was discussed. The homologous animal model should be pursued, if possible and feasible particularly for proof-of-principle studies. It may be required to develop a new animal model if existing homologous animal models are not relevant. For embryonic stem cell-derived products the relevance of a homologous animal model was generally questioned. Some *in vitro* models utilising human tissues for example, may add some important information that may not be obtained from homologous animal models. In addition, the use of the human stem cell-based medicinal product in an immunocompromised animal can provide important safety information generated with the actual human product. Large animal models may be necessary when a complex surgical procedure is not feasible or comparable in a rodent model. In addition larger animal models are useful in the exploration of long-term toxicity.

4.3. Topic 3: Biodistribution and Niche

4.3.1. Composition of Panel

Chair: Prof Asterios Tsiftoglou (CAT, CPWP)

Dr Egbert Flory, Head of the Section Somatic Cell Therapeutics & Tissue Engineering, CAT member, CPWP Vice-chair

Prof Kathryn Wood, Professor of Immunology at Nuffield Department of Surgery, University of Oxford

Dr Denis Corbeil, Group Leader at Tissue Engineering Laboratories of Biotechnological Centre, Technical University Dresden

Dr Ross Hawkins Head of cell production & diagnostics, division of cell biology, NIBSC

4.3.2. Questions raised & discussed

Panelchair:

What microenvironmental (Niche) factors will regulate the cell-fate decisions for differentiation, localisation and adaptation into the target site?

How can the biodistribution patterns of delivered stem cells be studied/evaluated *in vitro* and *in vivo*?

How can the fate of stem cells be assessed in animals and patients?

Audience:

What's the best and more relevant marker to label cells and study long-term biodistribution and also to study debris without changing characteristics?

EMA classifies the risk of stem cell products on the basis of processes, differentiation ability, administration route and so on. We think it seems to be not fully understood the impact of manufacturing processes to identify the risk of each stem cell product. We would like to discuss about risk categorised in the Reflection Paper.

Do Adult MSC find their way to the homing site? What kind of Radio-nucleotide tagging is possible?

Does it make sense at all to conduct biodistribution studies in animals?

4.3.3. Summary of biodistribution/niche panel:

Aspects on the microenvironmental factors on cell differentiation, biodistribution patterns of delivered stem cells and techniques to follow cells *in vivo* were discussed in this Panel. It was identified that the microenvironmental/niche factors, which regulate cell-fate decisions include physical contact and cell-cell-interactions. The interaction of the cell product with the microenvironment is also dependent on the route of administration. For example, during administration into blood, adhesive properties of the cells for the purpose of interaction with the tissue are important.

Various bioimaging techniques based on NMR, luminescence or radioactivity as tracking agents can be used to image cell migration *in vivo*. For the time being, however, this is not possible in humans as the use of a tracking reagent has to be justified on the basis of safety/efficacy. Therefore, biodistribution should be studied in the animal and extrapolated as best as possible to the human situation.

4.4. Topic 4: Tumorigenicity

4.4.1. Composition of Panel

Chair: **Dr Egbert Flory** (CAT, CPWP)

Prof Toivo Maimets, Professor of Cell Biology and Director, Institute of Molecular and Cell Biology, University of Tartu, CAT member

Dr Jane S. Lebkowski, Senior Vice President and Chief Scientific Officer of the Regenerative Medicine Division, Geron Corporation

Dr Sophie Lucas, Head of Unit on tissues, cell and gene therapy products, AFSAPPS, CAT and CPWP member

Dr Heidrun Holland, Translational Center of Regenerative Medicine and Medical Faculty, University of Leipzig

Dr Arnaud Foussat, Director Research and Development, TxCell

4.4.2. Questions raised & discussed

Panelchair:

In order to evaluate the tumourigenic potential and extent of genomic instability do we require *in-vitro* and/or *in-vivo* studies?

Should human stem cells be studied in a suitable animal model (immune compromised) or should homologous animal-derived stem cells preferably be used?

How can we interpret the results of tumourigenicity studies?

Audience:

Can tumourigenicity of haematopoietic stem cells be evaluated following transplantation for haematopoietic reconstitution in NOD/SCID mice? i.e. should one only look for leukemic events?

The draft Guideline places a lot of emphasis on tumourigenicity. However, clear practical guidance on how to approach this for the different types of SC is missing.

From the reflection paper, the sponsor seems to be required to establish and maintain hESC or iPS cells using human feeder cells and passage the cells mechanically. This point should be discussed.

What's your advice on sex-dependant graft (i.e. Human male cells to be used in male mice; a mix of cells or of animals).

Using hESC products, can research grade cells from a clinical grade cell line be used for tox/tumourigenicity studies or do clinical grade cells from the same line have to be used?

Is there a defined methodology for performing tumourigenicity studies in animal models? How long one needs to monitor the animals?

To confirm that EMA requires the sponsor to conduct the non-clinical studies using immuno-suppressed or constitutively immuno-deficient animals to evaluate some issues other than tumourigenicity of stem cell products. Whereas we understand the necessity for tumourigenicity tests using immuno-suppressed or constitutively immuno-deficient animals, it remains unclear whether to conduct tests other than tumourigenicity test in immuno-suppressed or constitutively immuno-deficient animals.

Line 218 (of Draft Reflection paper on stem cell-based medicine products (EMA/CAT/571134/2009)) it is not sensible to test tumourigenicity for every intermediate (and difficult to define what constitutes a manufacturing intermediate in this context). Tumourigenicity of only the end product should be tested since it is the only one that might have an impact on patient safety.

Line 264 – 268 (of Draft Reflection paper on stem cell-based medicine products (EMA/CAT/571134/2009)). Teratoma formation by pluripotent lines and tumour risk by MSCs are not at all comparable. One is passage-independent and the other one highly dependent on passage (and more easily avoidable). This fact should be considered to reword this paragraph.

4.4.3. Summary of tumourigenicity panel:

This Panel discussed the requirements to study tumourigenic potential. Panellists expressed their view that both *in vitro* and *in vivo* studies would be needed in order to obtain information on the level of risk of the stem cell-based medicinal product. General features of the cell population such as growth factor dependency and regulatory pathways can be studied by conventional *in vitro* methods and molecular technology. Homologous animal models may be helpful to add information on functional assays and long term toxicity. However, differentiation protocols are specific to animal cells; therefore, the human product should preferably be tested for tumourigenicity.

Panelists pointed out that it is likely impossible to separate tumourigenic cells from non-tumourigenic cells as it appears more and more likely that pluripotency and tumourigenicity are interconnected. Hence, results from tumourigenicity studies should be interpreted with caution. Absence of tumourigenic signals does not imply a lack of tumourigenicity. The extrapolation from animal tumourigenicity data to humans is particularly challenging and final proof can ultimately only be obtained from clinical trials. Nevertheless and to address this uncertainty, clinical trials should only be initiated on the basis of a positive risk-benefit ratio. Suspension rules, a cautious dosing approach and the ability to closely monitor for safety and tumourigenicity should be included into the clinical trial protocol.

4.5. Topic 5: Clinical aspects

4.5.1. Composition of Panel

Chair: Prof Giovanni Migliaccio (CAT, CPWP)

Prof Andreas Zeiher, Professor of Medicine and Chairman of the Dept. of Medicine at the Goethe-University in Frankfurt

Prof Paolo De Coppi, Paediatric Surgery Unit, University College London Medical School, London

Dr Gopalan Narayanan, Expert medical assessor with the biotechnology unit, MHRA, CAT & GTWP member

Dr Romaldas Mačiulaitis, Associated Professor, Clinical Pharmacology, Kaunas Medical University, Kaunas, Lithuania, CAT, CHMP, CPWP, PDCO member

Ms Elona Baum, Attorney and General Counsel for the California Institute for Regenerative Medicine, San Francisco, USA

4.5.2. Questions raised & discussed

Panelchair:

In cases where suitable homologous animal models or other relevant preclinical models are not available, how should the dose for the First-in-Man clinical studies be defined?

Is it possible and ethical to perform dose finding studies with stem cell-based medicinal products?

The physiological regulation of stem cells is reported to be dependant on the age and sex of the recipient. To which extent does the patient population enrolled in the clinical trials have to reflect this concern?

Specific safety issues, including lack of efficacy, should be evaluated in long term follow-up.

How long should the follow-up for products containing multipotent stem cells be?

Audience:

What methods of clinical evaluation can be used to compare treatments that offer a potential cure of a disease compared to alternative treatments, which are aimed at the long-term management of a chronic condition? Do we need new health assessment methods to do this?

Is it not necessary to design separate rules for allogenic and autologous clinical trials and treatments?

Compared to bone marrow, what are the Alternative MSC sources for specific diseases? Also what is their therapeutic potential (E.g. Wharton's jelly, adipose tissue, Dental pulp MSCs role compared to bone marrow)? What is the success rate and shelf life of MSC therapy for a specific disease (i.e. diabetes)?

How do EMA expect to approach paediatric population with ATMP?

"For tissue engineered products for which long term efficacy is claimed, a prolonged post-marketing follow-up might be required."

We also understand the necessity of long-term follow-up, but it seems to be difficult to provide examples of long-term follow-up (e.g. timing, interval, test method). We would like to discuss on the protocol of long-term follow-up.

Would autologous adult stem cell in vitro expansion (for clinical use) be considered as substantially modified cells or minimally manipulated?

How, in practical terms can allogeneicity be considered (i.e. Pre- injection selection / screening, Immunomonitoring pre/post transplant, technique, Schedule, Immunosuppressive therapy, In patient care).

Which disease conditions are likely going to hit the market first using a stem cell product?

What criteria do we need to meet to conduct clinical trials in Europe for Adult stem cell products (i.e. bone marrow, Wharton's Jelly or adipose tissue derived) developed in India or other countries.

How long is prolonged follow-up? Does this differ for patients in clinical trials versus patients receiving the marketed product?

Markers/tracers of cells might be desirable from a clinical perspective but will increase the risk from a quality point of view. Is GFP tagging or the like appropriate?

4.5.3. Summary of clinical panel:

Aspects around the design of clinical trials, dose and duration of follow-up were discussed in this Panel.

The Panel was of the opinion that it is necessary to perform dose finding studies with stem cell-based medicinal products. Depending on the disease and the niche, however, the dose can be very different. Likewise, within the same indication, the dose can also vary considerably from patient to patient, depending on individual physiological and pathophysiological criteria of the patient such as

inflammation. In general, the first-in-human dose should follow the same approach as for biologicals where no relevant animal model exists.

The Panel discussed the impact of the sex and age for stem cell treatments using iPSC and hESC. On a cellular level, both hESC and iPSC are very young and are not yet expressing genes related to the differentiation status of the future tissue. With respect to the sex it appears that the biological trigger and hormones related to male/female phenotype are also developed much later and hence the same sex of the recipient and donor may not be a requirement.

The duration of follow-up for products containing multipotent stem cells shall be determined on a case by case. No estimate relevant for all indications and products can be made.

The regulator will pay attention that the claim for efficacy in terms of duration of effect is supported by the data of the claimed period of effect. In addition the long-term follow-up requirement depends on the patient population and the risk perceived.

5. Conclusions

About 240 participants, including European and international experts from academia, regulatory authorities (Europe, Japan and the United States) and pharmaceutical industry, exchanged their experience and views on the scientific requirements, opportunities and challenges in the development of stem cell-based therapies.

The attendees of the workshop welcomed this opportunity to discuss the draft reflection paper on stem cell-based medicinal products. The conclusions reached on the quality, non-clinical and clinical sections will be considered when finalising the paper. Any further comments are welcome until 30 June 2010. The reflection paper is expected to be finalised by the end of 2010 and will be published on the Agency's website. The Agency will continue its public dialogue with academia, regulators and pharmaceutical industry on stem cell-based therapies.