ESF Exploratory Workshop:
Cell therapy: Consensus Workshop on Standards
Genova, Italy, Sept 6-8, 2003

SCIENTIFIC REPORT

Executive Summary

The first day of the workshop consisted of introductory lectures, which were open also to participants of the 2nd Annual Meeting of the European Tissue Engineering Society organised in Genova immediately prior to the workshop. Dr. Charles Kessler from EC first described the key aims, features and new instruments of FP6. He then described the possibilities to support stem cell research under FP6. In response to the first call, contract negotiations are under way with three projects where stem cells and cell therapy are key features. In the second call, two topics for integrated projects (IP), one for a network of excellence (NoE) and three for specific support actions (SSA) are related to stem cell research. Finally, he described the situation regarding support for human embryonic stem cell research through FP6. The Commission has made a new proposal which states that research on surplus embryos produced before June 27, 2002 (the launching date of FP6) could be supported if a number of other criteria are also fulfilled. Decision on this issue must be made before Dec 31, 2003.

Next Dr. Eero Vuorio (FI) presented ESF and EMRC focusing on the instruments available to support the theme of the workshop in its future directions. He later described in more detail the ESF plan to establish a EUROCORES Stem Cell Toolbox programme, which contains many of the same elements as in the project for FP6. Dr. Vuorio also briefly described the International Stem Cell Forum organised under Medical Research Council of UK, where the emphasis is clearly on registering, characterisation and banking of human embryonic stem cell lines.

The next two speakers, Dr. Yann Barrandon (CH) and Dr. Rodolfo Quarto (IT) gave state-of-the-art lectures of two areas of stem cell research, engineering of epidermis and bone marrow stromal cells, respectively. Both speakers focused on the challenges the field is facing. This includes a paradoxical situation that European Governments and EU are creating in Europe. On one hand they support basic and applied research of cell therapies, but on the other hand, they create an ever increasing number of hurdles (e.g. very strict GMP rules for academic research) and refuse sufficient financial support for the clinical trials needed to make use of the new therapies. Another issue of considerable confusion is the lack of uniform terminology for the different stem cell types. This of course mainly stems from lack of markers to characterise such cells.

Next, Dr. Anders Lindahl (SE) described the process of isolating human embryonic stem cells and assays used for their characterisation. In addition to the highly variable ethical environment in the member states, other challenges of human embryonic stem cell research include their laborious culture methods, the heterogenous nature of existing stem cell lines, their growth history on animal feeder cells, and the possibility of teratoma formation upon their introduction into the recipient.

Regulatory issues probably form the most challenging issue regarding clinical application of stem cells, cell therapy and tissue engineering. Four speakers addressed this complex issue. Dr. Malcom Moos (USA) from the Center for Biologics Evaluation and Research, Food and Drug Administration (FDA) described the development of the regulatory measures, which are particularly problematic in cell therapy and tissue engineering due to the many unknown risk factors that cannot be overlooked. A specific concern of regulatory agencies is the fact than unlike in conventional drug therapy (where the effect reduces time-dependently) the effect of cell therapy increases with time as the cell population propagates *in vivo* with no clearly defined end point. Another concern of regulatory agencies is the lack of specifications regarding the cells to be used for therapy. He urged scientists to focus on the characteristics rather than markers of stem cells, and to think of novel characteristics for stem cell populations. Dr. Jean-Hugues Trouvin (FR) from the French directorate for the evaluation of medicinal and biological products (Afssaps) described the French approach towards regulation of cell therapies. The aim is to protect the patient and estimate the risk/benefit -ratio. The system is based on authorisation of laboratories for cell therapy based on demonstration of their performance. Dr Frank Luyten (BE) presented a clinical perspective to cell therapy. Among the problem areas he emphasised were the efficacy, toxicity, safety and ethics of cell therapy. Combined with variability in the patient population, therapeutic method, type of operative procedure and rehabilitation these factors introduce a large number of variables which makes interpretation of the results from clinical trials difficult. European guidelines are badly needed to regulate the field. He emphasised that the new directives under preparation by DG Enterprise (Pharmaceuticals and Devised Units) and DG Sanco seem to contain unfortunate discrepancies, which may cause further confusion in the field in Europe. Finally, Dr. Fabio Marazzi (IT), a lawyer, described the legal situation focusing on the Italian legislation.

After the session the audience participated actively in the discussion.

The second and third days of the workshop (restricted to workshop participants and observers) focused on the expected practical outcome of the workshop, an application for the second call of FP6 on stem cell research. The specific topic of interest in the call reads:"Design of rational protocols for safety, quality and standardisation of stem cells and establishment of a European registry of stem cell".

The first morning professor Ranieri Cancedda (IT) presented his proposal for the structure of such an application. The proposal prompted a very lively discussion of the scientific content and an even more lively discussion of the terminology used. This was particularly affected by the opinions of the experts representing regulatory agencies. In line with the spirit of FP6, the meeting also discussed the involvement of Small & Medium size Enterprises (SMEs), particularly in respect to their role (partner *versus* contractor) in the proposal.
For the afternoon of the second day, workshop participants were divided into smaller groups to work on their specific areas of expertise using the proposed work packages of the FP6 proposal as the basic document.
The third day of the workshop (morning session only) focused on summarising the points raised by the working groups.

Details of the proposal are given in the scientific content of the event section.

During the workshop, Dr. Vuorio also presented the EUROCORES Stem Cells Toolbox as an alternative approach to obtain funding for the project.
At the same time, he also encouraged all participants to think about other instruments, e.g. those of ESF/EMRC, to support the activities described in the proposal outline.
In addition Dr. Claudio Lombardo (IT) presented a report on the European Economic Interest Grouping (EEIG) and "Liaison Group for Cancer (EEIG-LINC)". EEIG is a legally recognised partnership for trans-national collaboration for preparation of projects, such as stem cell research. Membership of EEIG includes universities, research institutes etc. He described the Organisation of European Cancer Institutes (OECI) as a model for networking of cancer centres, with an aim to establish a virtual European cancer institute. Although OECI has wide coverage, notable exceptions also exist in the current organisation. Dr. Lombardo proposed that the stem cell proposal be prepared in a similar fashion taking advantage of EEIG. More information can be obtained through the LINC web site (http://geie-linc.org) or by contacting Dr. Lombardo.

Scientific Content of the Event

The aim of the workshop was defined as establishment of a common European vision regarding methods in use to identify and isolate stem/pluripotent cells from different adult tissues. Optimisation of the protocols for the use of tissue engineering products in cell therapy and tissue regeneration is considered very important for their successful introduction into clinical practice (regenerative medicine).
Following is a summary of the submitted application for the second call of FP6 on stem cell research. The scientific content of this proposal was defined during and must be considered the main result of the ESF workshop:
“There is an increasing need for high standards for human stem cells (SCs) intended for clinical application to guarantee the highest protection level of human health. Establishment of common European directives will guarantee European citizens the same quality standards of SC products, regardless the member state in which they are obtained. Eurostem goals are: i) to perform pre-normative research to establish protocols and standards for safety and quality of SCs from different sources; ii) to establish a SC European registry and public cell banks of differentiated and undifferentiated cultured SC lines under GMP conditions in cooperation with other existing initiatives. Adult SCs from epithelia and mesoderm derived tissues, are the object of this proposal. Already existing human embryonic and neural SC lines are considered as research tools to investigate mechanisms regulating SC self-renewal (WP5). Partners with an internationally recognised expertise in basic biology and clinical application of adult SCs will define and qualify scientific indicators needed for validation of cultivation methods of SCs for cell therapy (WP1). The *in vivo* efficacy of selected adult SCs preparations cultured according to GMP conditions will be first assessed in animal models (WP3). Immunomodulatory properties and potential immunogenicity of allogeneic SCs will be investigated in WP2. Cell manipulation procedures established in WP1 will be reviewed according to cGMP and a general strategy for the production, testing and validation of products for cell therapy in Europe will be defined (WP4). A SC registry will be established; standards and procedures for SC banking according to European Parliament Directive 2003/C 240 E/02 will be defined (WP6). Goal of WP7 is to provide the best possible scientific advice to national and European regulatory bodies in adapting legislation and guidelines to continuous scientific and technical progress.

Major effort will be put in education and training of operators/end users (lab scientists and technicians; SMEs, physicians and surgeons) and in knowledge spreading (WP8). A workpackage (WP10) is dedicated to exploitation and technology transfer. An external independent Ethics Committee will monitor all project activities."

Assessment of the results, contribution to the future direction of the field

A proposal for the second call of the 6th Framework Programme (FP6) of the European Commission (EC) was drafted further to the workshop.

The outcome of the workshop can be also considered as an input and as material for both European and National Regulatory Agencies.

Final Programme (see enclosure # 1)

Final List of Participants (see enclosure # 2)

Statistical Information on Participants

Average age of participants: 48.6

Countries of Origin:

Belgium (2),
France (3),
Germany (3),
Israel (1),
Italy (6) (including convenors),
Netherlands (1)
Sweden (3),
United Kingdom (2)
United States (1)

Encl. 1

Saturday 6 September 2003

Magazzini del Cotone, Porto Antico – Levante Room

Open participation by on-site free registration

Afternoon (14.30-17.30)

Symposium: Establishing a common European vision

(Chair: Ranieri Cancedda)

Introduction

R. Cancedda, *10'*

The stem cell research in the 6th European Framework Programme for Research and Technological Development

C. Kessler, *15'*

Presentation of the ESF – EMRC

M. Toth, E. Vuorio, *10'*

Adult stem cells from bench to bedside

Epithelia, Mesoderm derived tissues, Nervous tissues

Y. Barrandon, R. Quarto, *30'*

Embryonic stem cells

A. Lindahl, *15'*

Ethical and regulatory issues

F. Luyten, F. Marazzi, M. Moos Jr, J.H. Trouvin, *60'*

Scheduled interventions by the audience

20'

Open Discussion

20'

Sunday 7 September 2003

Istituto Nazionale per la Ricerca sul Cancro,
Advanced Biotechnology Centre
Invited participants only

Morning (09.30-12.30)

Plenary Session: A European network on stem cell research

The experience of the GEIE "Liaison Network for Cancer"
C. Lombardo

Open Discussion

Lunch

Afternoon (14.00-17.00)

Working Groups

- **Autologous adult stem cells from different tissues - Qualification of adult stem cells for clinical applications**
- **Management**

- **Autologous adult stem cells from different tissues - Qualification of adult stem cells for clinical applications**
- **Regulatory and ethical issues**
- **Education and Training**

Monday 8 September 2003

Istituto Nazionale per la Ricerca sul Cancro,
Advanced Biotechnology Centre
Invited participants only

Morning (09.30-12.30)

Plenary Session: Future plans of activities

The European Science Foundation Scientific Networks and Programmes
E. Vuorio

Conclusions

Main Objectives of the Workshop:

Studies are currently being carried out to identify and isolate stem/pluripotenti progenitor cells from different adult tissues. Development of these studies and validation of new protocols for the use of tissue engineering products in cell therapy and tissue regeneration can be considered as an ideal integration of substitutive surgery. Through this Consensus Workshop on Standards in Cell Therapy it is expected to establish a common European vision. The outcome of the workshop can be also considered as an input and as material for both European and National Regulatory Agencies.

Encl. 2

Final List of Participants

Convenors:

1. **Professor Ranieri CANCEDDA**
Lab.di Medicina Rigenerativa - Istituto Nazionale per la Ricerca sul Cancro
Genova, Italy

2. **Professor Rodolfo QUARTO**
Department of Oncology, Biology and Genetics - The University of Genova
Genova - Italy

ESF Representatives: European Medical Research Councils (EMRC)

3. **Dr. Miklos TOTH**
Hungarian Academy of Sciences, Hungarian Scientific Research Fund (OTKA)
Budapest - Hungary.

4. **Professor Eero VUORIO**
Department of Medical Biochemistry and Molecular Biology
Univesity of Turku - Turku, Finland

5. **Dr. Thomas BRUHN**
Observer, representing the *EMRC Chairman*, Prof. Clemens Sorg

Participants:

6. **Professor Yann BARRANDON**
Dept. of Experimental Surgery – CHUV - Lausanne University Hospital
Lausanne - Switzerland

7. **Dr. Mats BRITTBERG**
Centre for Musculoskeletal Tissue Engineering - Institution of Orthopaedics –
Göteborg University – Kungsbacka, Sweden

8. **Dr. Lee BUTTERY** (in place of Dame Professor Julia Polak)
Tissue Engineering and Regenerative Medicine Centre - Imperial College School of Medicine
London, United Kingdom

9. **Mr. Pasquale DE BLASIO, Eng.**
Centre for bio-molecular Interdisciplinary Studies and Industrial Application (CISI)
University of Milan - Segrate (MI), Italy

10. **Dr. Michele DE LUCA**
Fondazione Banca degli Occhi del Veneto
Venezia-Mestre, Italy

11. **Dr. Michaela ENDRES**
Tissue Engineering Laboratories, Medical Faculty Charite
Berlin, Germany

12. **Professor Dan GAZIT**
Skeletal Biotech Lab - Hebrew University of Jerusalem - Hadassah Medical Centre
Jerusalem, Israel

13. **Professor Timothy E. HARDINGHAM**
UK Centre for Tissue Engineering, Universities of Manchester and Liverpool
University of Manchester – Manchester, United Kingdom

14. **Dr. Charles KESSLER**
General Direction Research, European Commission
Brussels, Belgium

15. **Professor Anders LINDAHL**
Institute of Laboratory Medicine, Department of Clinical Chemistry and Transfusion Medicine
Sahlgrenska University Hospital – Göteborg, Sweden

16. **Dr. Claudio LOMBARDO**
Scientific Attaché, Italian Embassies in Belgium, Luxembourg and NATO
Brussels, Belgium

17. **Professor Frank LUYTEN**
Professor and Chairman, Department of Rheumatology - UZ Leuven
Leuven, Belgium

18. **Mr. Fabio MARAZZI, Dr. in Law**
Member, Science, Biotechnology and Bioethics Committee of the American Bar Association
Vice-President, Contracts Commission of the Union Internationale des Avocats, Paris
Bergamo, Italy

19. **Dr. Malcom MOOS**
Center for Biologics Evaluation and Research - Food and Drug Administration
Rockville, MD - United States.

20. **Dr. Hervé PETITE**
Laboratoire de Recherches Orthopédiques, UMR CNRS 7052 – Université D. Diderot
Paris, France

21. **Dr. Jochen RINGE**
Tissue Engineering Laboratories - Medical Faculty Charite, Berlin
Berlin, Germany

22. **Professor Michael SITTINGER**
Tissue Engineering Laboratories - Medical Faculty Charite, Berlin
Berlin, Germany

23. **Dr. Tommi TALLHEDEN**
Research Centre for Endocrinology and Metabolism, Sahlgrenska University Hospital
Göteborg, Sweden

24. **Professor Jean Hugues TROUVIN**
Directeur de l'Évaluation des Médicaments et des Produits Biologiques,
Agence Française de Securite Sanitaire des Produits de Sante
Saint-Denis, France

25. **Professor Gerard WAGEMAKER**
Erasmus Universiteit Rotterdam -Institute of Hematology
Rotterdam, The Netherlands

Organizing Secretariat

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