



EUROPEAN UNION



ROMANIAN GOVERNMENT



Structural Funds
2007-2013

Project no. 852, SMIS Code 14676
Centre for Gene and Cellular Therapies in the Treatment of Cancer – ONCOGEN
POSCCE-A2-O2.2.1-2009-4



ONCOGEN
Centre for Gene
and Cellular Therapies
in the Treatment of Cancer

EXPERIENCE IN FP7 RESEARCH PROJECTS

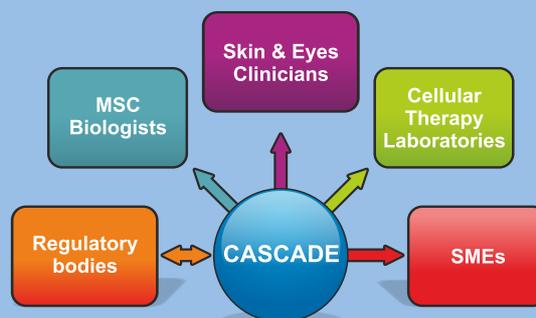
Cultivated Adult Stem Cells as Alternative for Damaged tissue - CASCADE

Identification number: FP7-223236, CE (Call FP7-Health-2007-1.4-7)
Implementation period: 1.12.2008-30.11.2011
Project Coordinator: Luc Sensebé (France) and Hermann Eichler (Germany)
Coordinator for Romania: Carmen Bunu Panaitescu (cbunu@umft.ro)

Partners:

France: EFS (coordinator), INSERM, CNRS, ABCELL-BIO, OTR3, ALCIMED; **Germany:** DRK, Saarland University, UULM, Heidelberg University; **Italy:** Policlinico Milano, Verona University, Biotrack; **Romania:** UMFVB Timisoara; **UK:** Oxford University, CellTran Ltd-Sheffield University

Overview of CASCADE



UMFVBT Project team:

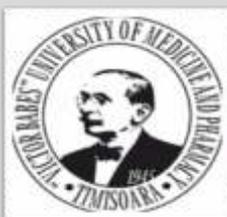
Carmen Bunu Panaitescu, Virgil Paunescu, Gabriela Tanasie, Alexandra Enache, Cristina Dragomirescu, Mihaela Galanton, Carmen Tatu, Daciana Nistor, Florina Bojin, Erika Deak, Calin Muntean, Laura Marusciac, Gabriela Basaraba, Carmen Pitic.

Objectives:

The main objective of the proposed work is to develop standardised GMP methods of culturing adult mesenchymal stem cells (MSC) for clinical application for repairing damaged human tissue: MSCs derived from different sources will be used: bone marrow (BM), umbilical cord blood (CB), adipose tissue (AT), or amniotic membrane (AM). The therapeutic potential and the function of cultured MSCs will be evaluated extensively in vitro and in vivo. The consortium will develop clinical protocols for MSC applications in defined diseases related to chronic wound healing (chronic venous leg ulcer and corneal ulcer).

Work package 3 Ethic, regulatory, legal issues and dissemination

WP 0
Management and administration



WP 1

Translational
R&D GMP
Production

WP 2

Mechanisms
of repair
and validation

WP 3

Ethical, Regulatory, Legal
and dissemination Issues



WP 4

Clinical targets
and protocol
definition

Final
outcome

Ethical issues

Analyze work within WP1 and WP4 to match perfectly to the ethical and regulatory rules implemented at national and European level.

Regulatory issues

Apply for authorization from regulatory authorities at European and national level. Organize annual workshops integrating key people of national and European regulatory authorities and ethical experts.

Legal issues

Survey on guidelines, rules and laws in cellular therapeutics and discuss identified problems with national and European authorities.

Dissemination of knowledge

Patent survey and application, set-up of an educational program, organization of annual international workshops on MSCs, and providing general information to the public.





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CASCADE PARTNERS



The four workpackages (WPs) will focus on various issues:

WP1

Translational R&D and GMP production - Leader: Policlinico Milano

- Starting materials and separation of stem cells (BM, CB, AT, AM);
- Culturing of stem cells in GMP conditions;
- Controls (sterility, identity, genetic stability, potency, immune-reactivity, donor validation).

WP2

Mechanisms of Repair and Validation - Leader: DRK

- Testing MSC functionalities and efficacy by *in-vitro* and *in-vivo* models:
 - *in vitro*: collagen type I-3D-culture; AM use for repopulation by MSC and use as a delivery system for administration of MSC; MSC – epithelial corneal cells co-cultures for corneal repair;
 - *in vivo*: MSC-induced wound healing in non-diabetic and diabetic nude mice, AM patch, β 2-integrin deficient mouse model;
 - MSC-EPC (endothelial progenitor cell) interaction;
- Immunological consequences of stem cell use (MSC and innate immune system, MSC and adaptive immune response);
- MSC trafficking studies.

WP3

Ethic, regulatory, legal issues and dissemination - Leader: UMFVB Timisoara

- Ethical and legal issues regarding the stem cell use for basic and clinical research;
- Regulatory issues – national approaches within EU countries on stem cell therapies;
- Dissemination and exploitation of knowledge.

WP4

Towards clinical studies on the safety and efficacy of mesenchymal stem cell transplantation for the treatment of skin and corneal chronic ulcerations – Leader: INSERM

- Construction of the CASCADE European clinical networks in dermatology and ophthalmology;
- Validation of the clinical targets of wound healing impairment in dermatology (venous leg ulcer) and ophthalmology (chronic corneal ulcer);
- Construction of clinical studies protocols for validation by ethical committee and regulatory authorities.



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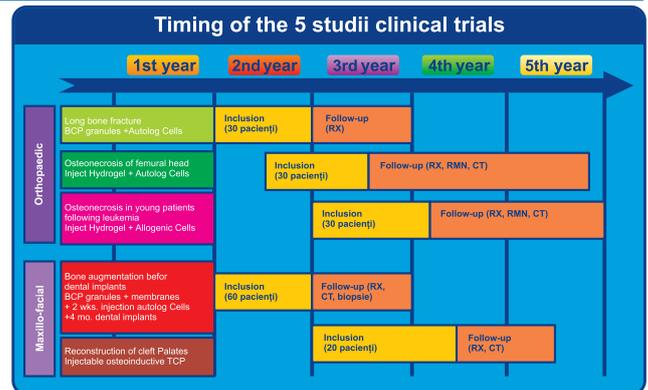


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EXPERIENCE IN FP7 RESEARCH PROJECTS

Regenerating Bone defects using New biomedical Engineering approaches - REBORNE

Identification number: FP7-241879
(call HEALTH-2009-1.4-2)
Implementation period: 1.01.2010-31.09.2014
Project Coordinator: Pierre Layrolle (France)
and Luc Sensebé (France)
Coordinator for Romania: Prof. Dr. Carmen
Bunu Panaitescu (cbunu@umft.ro)



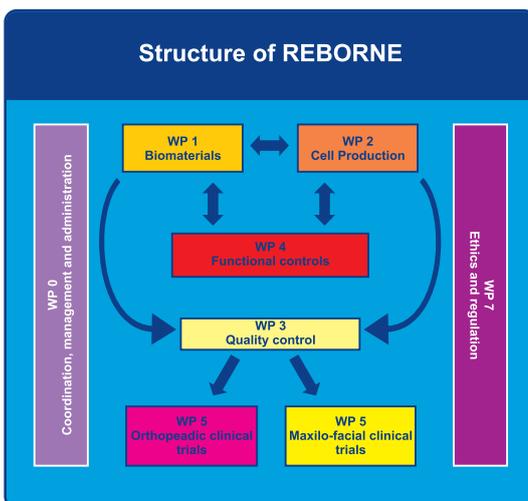
Partners:

France: INSERM (coordinator), EFS, BIOMATLANTE, CEA, CHU NANTES, CHU TOURS, AP-HP, ALCIMED; **Italy:** Policlinico Milano, UNIMORE, Verona University, IOR, AOU MEYER; **Belgium:** KITO, Liege University; **The Netherlands:** XPAND, UMC UTRECHT; **Spain:** UPC, UAM; **Romania:** UMFVBT; **Germany:** UNITUE, UULM, Max Planck Institute; **Norway:** Bergen University

UMFVBT Project Team:

Carmen Bunu Panaitescu, Virgil Paunescu, Gabriela Tanasie, Carmen Tatu, Daciana Nistor, Florina Bojin, Laura Marusciac, Fabian Tatu, Dinu Vermesan, Mihaela Galanton, Cristina Dragomirescu, Gabriela Basaraba, Carmen Pitic

Structure of REBORNE



Objectives:

The objective of REBORNE is to perform clinical trials using advanced biomaterials and cells triggering bone healing in patients. In order to reach this goal, five phase II clinical studies with 20 patients are proposed in 12 clinical centres spread in 8 European countries. Three orthopaedic trials concerning the treatment of long bone fractures and osteonecrosis of the femoral head in adults or children will be conducted using bioceramics, hydrogel for percutaneous injection and stem cells from autologous or allogeneic sources. Clinical research will also concern maxillofacial surgery with bone augmentation prior to dental implants and the reconstruction of cleft palates in children. The safety and efficacy of the new therapies will be assessed clinically using X-rays, CT scans and MRI as well as histology of biopsies.

The seven work-packages (WPs) will focus on various issues, as follows:

WP1

Biomaterials – Leader: UPC

- Research and development of biphasic calcium phosphate ceramics as scaffolds for bone tissue engineering;
- Research and development of injectable bone substitutes with osteoinductive properties;
- Research and development of osteoinductive, angiogenic, high strength and resorbable composites.



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EXPERIENCE IN FP7 RESEARCH PROJECTS

WP2

Cell production – Leader: EFS

- Defining common GMP cell culture conditions for the first clinical trial;
- Choosing the most efficient protocol for the intermediate clinical trials;
- Establishing GMP cell culture protocols for newborn MSC;
- Establishing GMP cryopreservation protocols;
- Comparing the 3 MSC sources for allogeneic uses;
- Providing GMP grade cells for the clinical trials.

WP3

Quality control – Leader: POLICLINICO

- QC on the genotypic stability of bone marrow (BM), adipose tissue (AT), cord blood (CB) mesenchymal stem cells (MSC);
- QC on the functionality of BM, AT, CB MSC for bone regeneration;
- QC on the phenotypic profile of BM, AT, CB MSC;
- QC on immunosuppressive properties of BM, AT and CB MSC;
- QC on MSC-biomaterials combination;
- Testing refinements.

WP4

Functional controls – Leader: UNIMORE

- Establish improved potency assays for selected GMP-manufactured MP (Mesenchymal Progenitor) with biomaterials;
- Unification of animal MP culture conditions;
- Explore osteogenic potentials of native human MP in biomaterial combinations;
- Combining angiogenesis and osteogenesis for an improved bone regeneration;
- Impact of immunology and bone regeneration: providing insights for off-the-shelf MP;
- Mimicking challenging clinical trials of bone regeneration with animal models.

WP5

Orthopaedic clinical trials – Leader: UAM

- 1st Orthopaedic trial: Evaluation of efficacy of autologous MSCs combined to biomaterial to enhance bone healing in patients with delayed consolidation after long bone diaphyseal fracture, requiring graft apposition;
- 2nd Orthopaedic trial: Evaluation of efficacy of autologous MSCs to enhance bone healing in patients with early avascular necrosis of the femoral head;
- 3rd Orthopaedic trial: Evaluation of efficacy of allogeneic MSCs to enhance bone healing in patients with early avascular necrosis and previous haematologic malignant disease with immunosuppression.

WP6

Maxillofacial clinical trials – Leader: CHU NANTES

- Vertical and sagittal bone augmentation in the maxillar bone and mandible using calcium phosphate granules, membrane and autologous MSCs prior to dental implants;
- Reconstruction of cleft palates in adults or children using an osteoinductive injectable bone substitute

WP7

Ethic, regulatory, and legal issues and dissemination – Leader: UMFVBT

- Regulatory issues;
- Ethical issues;
- Legal issues;
- Dissemination and exploitation of knowledge.



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REGENERATIVE MEDICINE

Clinical applications of hematopoietic stem cells (HSC) in myocardial infarction

Projects:

- **Development of Cellular Therapies for *Diabetes Mellitus* - BETASTEM, VIASAN Programme,** contract no. 314/2004 (2004-2006).
- **Stem Cell Therapy for Vascular Regeneration and Reconstruction - ANGIOSTEM, CEEX - VIASAN Programme,** contract no. 44/2005 (2005-2008).
- **Development of Tissue Bioengineering Techniques for Myocardial Reconstruction - CARDIOSTEM, VIASAN Programme,** contract no. 311/2004 (2004-2006).

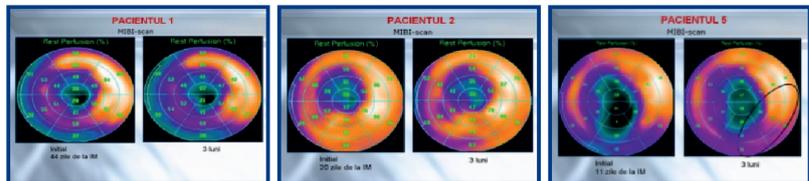
First clinical trial in Romania in cooperation with the Cardiovascular Diseases Institute

- **HSC isolation with CliniMACS**
- **administering in acute intracoronary myocardial infarction**
- **Recovery assessment: scintigraphy**

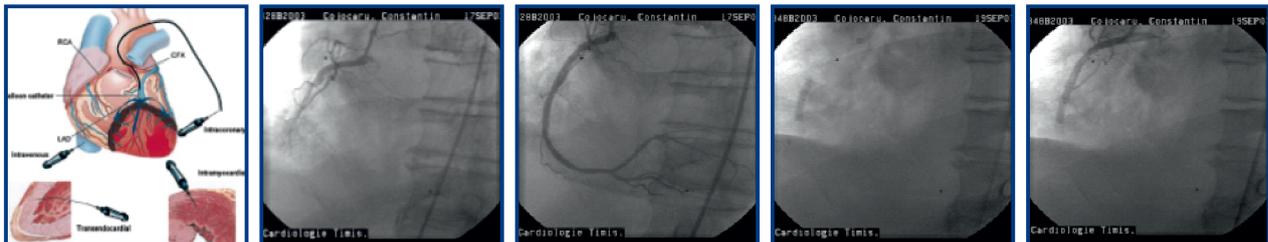
Bone marrow harvesting and HSC isolation



Recovery assessment



Intracoronarian administration of HSC AC133+



In vitro studies for assessment of mesenchymal stem cells potential in osteoarticular regeneration

Projects:

- **Development of Innovative Therapies for Osteoarticular Reconstruction - CELLART, CEEX - VIASAN Programme,** contract no. 45/2005 (2005-2008).
- **Development of Bio-Orthopaedics Innovative Therapies - BIOART, CEEX - VIASAN Programme,** contract no. 70/2006 (2006-2008).
- **Reconstruction of Segmental Bone Defects through Biomimetic Matrices Colonised with Osteogenic Cells - RECON-OS, Partnerships in Priority Areas Programme,** contract no.41-091 /2007(2007-2009).



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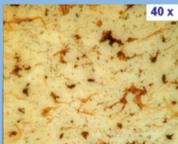
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REGENERATIVE MEDICINE

MSC are pluripotent progenitor cells able to differentiate in various skeletal cells, such as osteoblasts and chondrocytes.

In vitro and *in vivo* preliminary studies certify their potential to be used in clinical applications for osteoarticular disorders.

IN VITRO MSC DIFFERENTIATION INTO THE OBSTEOLASTIC



Von Kossa staining

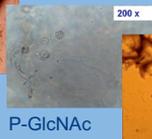


RT-PCR (14 days)

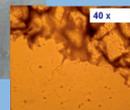
CELLS - SCAFFOLD INTERACTION



Nanoporous Silicium

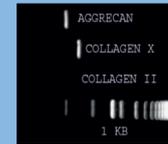


P-GlcNAc



polyGly-poliLactic

IN VITRO MSC DIFFERENTIATION INTO THE CHONDROCYTIC LINEAGE



RT-PCR (21 days)



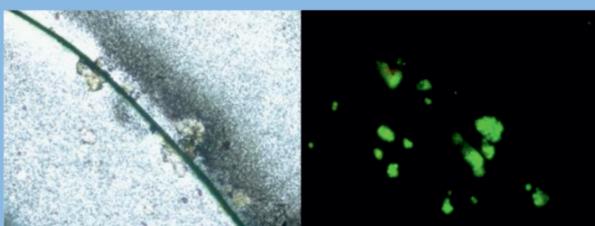
Cell growing around a metallic bar (titanium)

In vitro biocompatibility studies

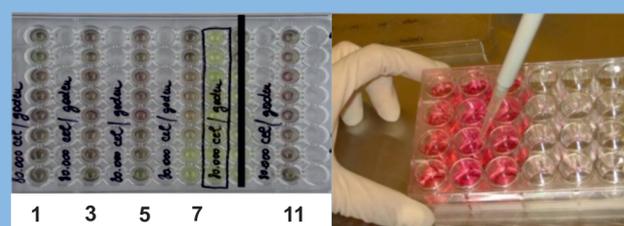
Projects:

- Obtaining by Alternative Methods of Metal Doped TiO₂ Nanocrystals. The Study of Potential Applications in Health, Biology and Environment, CEE X MATNANTECH Programme, contract no. 3/2005 (2005-2008).
- Nanocontrol and Multifunctionality in Materials, Microlayers and Shape Memory Architectures, CEE X MATNANTECH Programme, contract no. 7/2005 (2005-2008).
- **RONANOMED** National Nanomedicine Integrated Network, CEE X MATNANTECH Programme, contract no. 42/2005 (2005-2007).
- Complex Researches regarding the Acquiring and Magnetic Properties of Surfacted/Non-Surfacted Biocompatible Co_{0.7}Fe_{3.3}O₄ Ferromagnetic Nanoparticles Systems with Potential Applications in Cancer Therapy - **NANOPART**, project 071-025, funded through PNCDI-II, Partnerships Programme, 2008-2010

In collaboration with Romanian partners methods for *in vitro* compatibility studies were developed which are currently under review for standardisation.



HEK cells on NiTi alloy. Cells are attached, alive and proliferative
Left panel - visible light, right panel - fluorescence, ob.10x



Biocompatibility test



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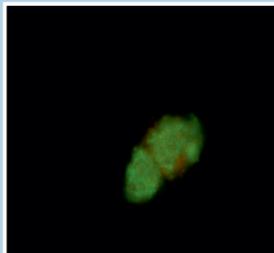
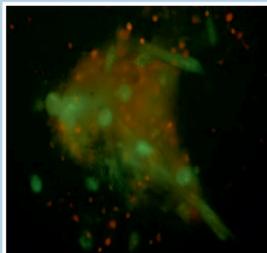
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INNOVATIVE THERAPIES IN CANCER

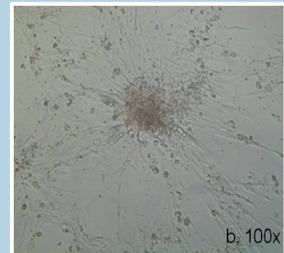
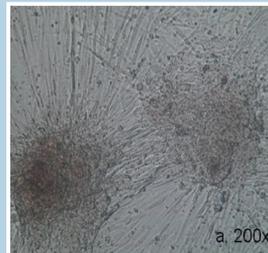
Tumor Cells Isolation and Characterisation

Projects:

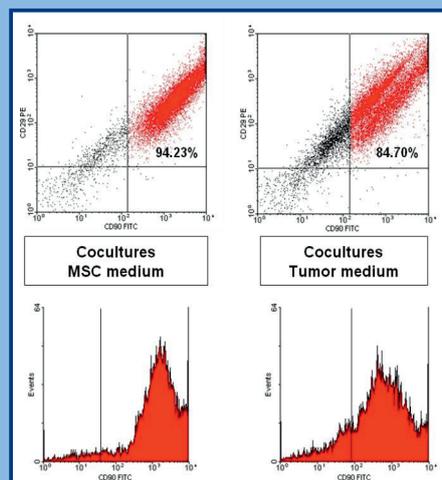
- Experimental Studies on Human Transfected Mesenchymal Stem Cells to Develop an Innovative Therapeutic Strategy for Glioblastoma - **GLIOSTEMCELL**, CEEX Programme Module I, contract no. 176/2006 (2006-2008)
 - Tumour Neural Stem Cells: A New Therapeutic Target in the Multimodal Treatment of Malignant Cerebral Gliomas - TUMORSTEM, project 041-035, funded by PNCDI-II, Partnerships Programme, 2008-2010
- Cells were isolated from solid tumours by various enzymatic techniques
 - Tumor cells characterisation: immunophenotyping, co-cultures with MSC, proliferation and apoptosis tests



Vital staining tumor cells



Morphological aspects of cocultured cells after 1 and 2 weeks, respectively





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INNOVATIVE THERAPIES IN CANCER

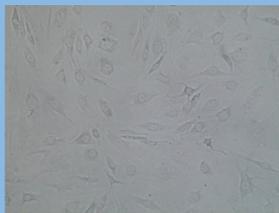
Isolation and Complex Characterisation of TAF (Tumor Associated Fibroblasts)

Project:

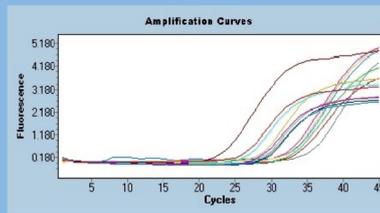
- Genetic Engineering of Tumour Stem Cells in view of Immune Response Modulation in Non-Viral Cancers - ONCOSTEM, PN II – Partnerships Programme, contract no. 41-019/2007 (2008-2010)
- Complex TAF characterisation: immunophenotyping, secretory profile, adherence, pluripotent capacity, ultrastructural aspects



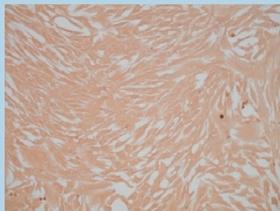
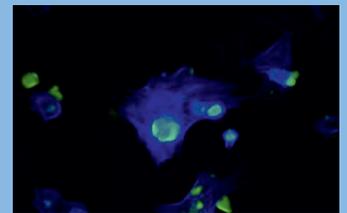
MSC



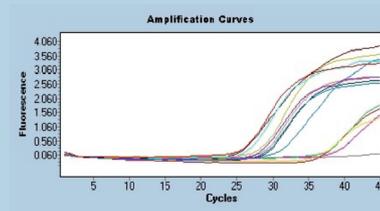
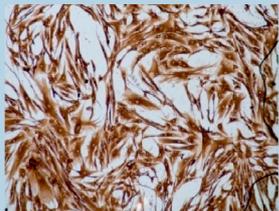
TAF



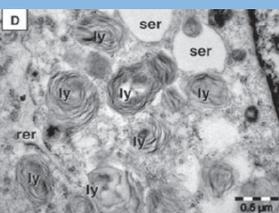
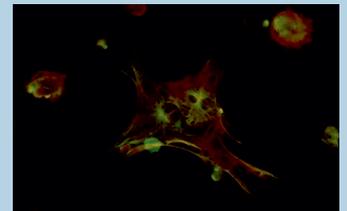
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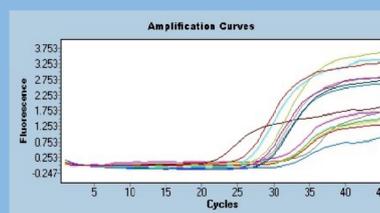
Vimentine Expression



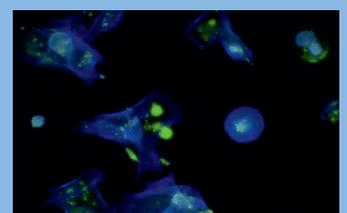
Sox2



Ultrastructural Aspects



Oct-4



TAF: pluripotent capacity