GENERAL INFORMATION

Grant Agreement number: **241879**

Project acronym: **REBORNE**

Project title: **Regenerating Bone defects using New Biomedical Engineering approaches**

Funding Scheme: **Collaborative Project (large-scale integrating project)**

Date of latest version of Annex I against which the assessment will be made:
Periodic report: 1st ☒ 2nd □ 3rd □ 4th □

Period covered: **from 01/01/2010 to 31/12/2010**

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SEVENTH FRAMEWORK PROGRAMME

Funded by the European Commissions 7th Framework Program

0 Table of Contents

1 Declaration by the Scientific representative of the Project Coordinator

I, as scientific representative of the coordinator of this project and in line with the obligations as stated in Article II.2.3 of the Grant Agreement declare that:

- The attached periodic report represents an accurate description of the work carried out in this project for this reporting period;

The project (tick as appropriate):
□ has fully achieved its objectives and technical goals for the period;
☒ has achieved most of its objectives and technical goals for the period with relatively minor deviations.
□ has failed to achieve critical objectives and/or is not at all on schedule.

- The public website, if applicable
☒ is up to date
□ is not up to date

- To my best knowledge, the financial statements which are being submitted as part of this report are in line with the actual work carried out and are consistent with the report on the resources used for the project (section 3.4) and if applicable with the certificate on financial statement.

- All beneficiaries, in particular non-profit public bodies, secondary and higher education establishments, research organisations and SMEs, have declared to have verified their legal status. Any changes have been reported under section 3.2.3 (Project Management) in accordance with Article II.3.f of the Grant Agreement.

Name of scientific representative of the Coordinator: Pierre Layrolle
Date: 25/ 02/ 2011

For most of the projects, the signature of this declaration could be done directly via the IT reporting tool through an adapted IT mechanism.

2 Publishable Summary

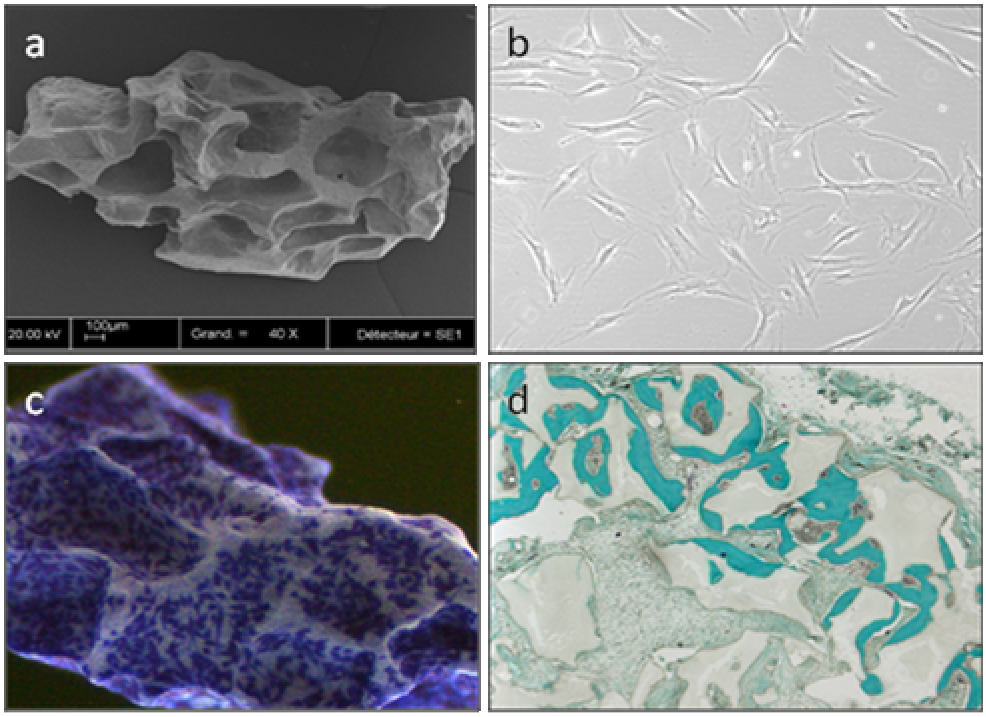
Bone is among the most frequently transplanted tissue with about 1 million procedures annually in Europe. The worldwide market of bone replacement materials is currently estimated at 5 billion € with a 10% annual growth. Autologous and allogenic bone grafts account for more than 80% of procedures in orthopaedic and maxillofacial surgery for reconstruction of skeletal defects. However, these biological grafts require a second surgical site with complications and cost, are limited in quantity and efficacy and may carry the risks of disease transfer and immunological rejection. Significant growth opportunities exist for synthetic bone substitutes in association with mesenchymal stem cells from autologous or allogenic sources as alternatives to biological bone grafts. The objective of REBORNE is to perform clinical trials in orthopaedic and maxillofacial surgery by using advanced biomaterials and cells triggering bone healing in patients. In order to reach this goal, five clinical studies with 20 patients are proposed in 12 clinical centres spread in 8 European countries.

In the first year of the REBORNE's project, the consortium has progressed very well with numerous pre clinical achievements that are of most importance for preparing clinical studies. For instance, the best suitable biomaterial to be used in the first orthopaedic and maxillofacial clinical trials has been selected. The biomaterial consists of macro and micro porous biphasic calcium phosphate ceramic granules being CE-marked and 510(k) FDA approved. The biomaterial is well-suited for supporting attachment and osteogenic differentiation of human mesenchymal stem cells (hMSCs). It is packaged in appropriate syringes for mixing at the time of surgery with GMP-produced hMSCs. During this year, other innovative biomaterials including chitosan hydrogels, osteoinductive ceramics and calcium phosphate cements have been developed.

Both the production and transportation of clinical batches of hMSCs have been standardized by GMP producers. The cell producing facilities have defined standard operating procedures to produce billions of hMSCs from bone marrow or adipose tissue harvests. For the safety of patients, xenobiotic substances like fetal calf serum have been replaced by human blood derivative (platelet lysate) during the production of batches of hMSCs. Both growth and osteogenic differentiation of hMSCs have been enhanced by using this medium. Furthermore, the dose of cell per ml of biomaterial for inducing ectopic bone formation in subcutis of nude mice has been determined. After subcutis implantation of hMSCs/MBCP+ hybrids, well-mineralized bone was observed in contact to the scaffold. It has been shown that culturing cells on biomaterial as well as the use of osteogenic factors such as dexamethasone or bone morphogenetic proteins were not a prerequisite for the formation of *de novo* bone tissue.

The clinical protocols for the first clinical trials in orthopaedic and maxillofacial surgery have been finalised. In orthopaedic surgery, long bone fractures will be treated using autologous hMSCs derived from bone marrow in combination with CaP granules. Similarly, clinical research will also concern maxillofacial surgery with bone augmentation using autologous hMSCs and biomaterials prior to dental implants. The safety and

efficacy of these new therapies will be assessed clinically using X-rays and CT scans as well as histology of biopsies. Ethical and regulatory issues have been well considered in both the pre clinical studies and the preparation of clinical protocols. In summary, the project REBORNE has progressed very well in the year 2010 with good collaboration between universities, SMEs manufacturing biomaterials, GMP-cell producing facilities and surgeons in hospitals.



Regarding socio-economic impact, the project REBORNE has contributed to the development of knowledge and competitiveness of Europe with the publication of scientific papers and presentations at international conferences. Additionally, the project allowed the recruitment of high qualified personal as indicated by an increase of 30% of human resources during 2010. The progresses to date have put the basements for future clinical trials opening the field of regenerative medicine with stem cells and biomaterials.

3 Core of the report for the period: Project objectives, work progress and achievements, project management

3.1 Projects objectives for the period

The objectives of the project REBORNE for the first reporting period were:

1. The selection of the most suitable biomaterial for the clinical trials ORTHO1 and MAXILLO1 in respect to biocompatibility, cell adhesion, osteogenicity and surgical handling.

2. The definition of standard operating procedures for the preparation of clinical lots of human mesenchymal stem cells in good manufacturing practice conditions and excluding the use of xenobiotic substances (e.g. foetal calf serum).

3. The determination of the cell dose and contact time in combination to biomaterial to induce *de novo* bone formation in small animal models.

4. The preparation of clinical protocols for ORTHO1 and MAXILLO1 including ethical issues and regulatory authorities demands.

3.2 Work progress and achievements

3.2.1 WP1 – Biomaterials

3.2.1.1 Summary of progress towards objectives and details for each task of WP1

The objectives of WP1 for **the first reporting period** were:

1. Research and development of biphasic calcium phosphate ceramics as scaffolds for bone tissue engineering including a specific packaging device for association with human mesenchymal stem cells (hMSCs).
2. Research and development of injectable bone substitutes based on hydrogels and calcium phosphate ceramic particles that will allow the injection of hMSCs and regeneration of bone defects.
3. Research and development of composites based on calcium phosphate cements that will have intrinsic osteoinductive properties, allowing for the incorporation of vascular and/or bone growth factors, supporting cell growth, having high strength and being resorbable.

To achieve the mentioned objectives, three tasks are included in WP1:

Task 1. Research and development of biphasic calcium phosphate ceramics as scaffolds for bone tissue engineering (INSERM #1, BIOMATLANTE #3, UPC #10)
Task 2. Research and development of injectable bone substitutes with osteoinductive properties (INSERM #1, XPAND #9, BIOMATLANTE #3, KITOZYME #8, UPC #10)
Task 3. Research and development of osteoinductive, angiogenic, high strength and resorbable composites (UPC #10, INSERM #1, XPAND #9, BIOMATLANTE #3, KYTOZYME #8, MPG #22).

In the following section, the progress of the work carried out within the first year for each Task, is reported.

Task 1. Research and development of biphasic calcium phosphate ceramics as scaffolds for bone tissue engineering

a) Work carried out by BIOMATLANTE #3

Production and characterisation of macroporous biphasic calcium phosphate (MBCP+) to be used in Ortho1 and Maxillo1 clinical trials

- Complete physico-chemical characterization of the MBCP+ granules (see deliverable D1-1)
- Production of a specific MBCP+ batch for clinical trial (10 kg)
- Characterization density MBCP+: Development of tools for evaluation of the real density of MBCP+ granules batches. Test of reproducibility

Moreover, BIOMATLANTE has supplied the MBCP+ granules to several partners, to perform different tests previous to the clinical trials:

- Validation of the clinical feasibility on cadaver using MBCP+ in syringe and collagen membrane (to be used in MAXILLO 1 clinical trial).
- Validation of the choice of the biomaterial + ancillary: Low pressure syringe containing 5 mL of 1-2 mm MBCP+ granules.
- Validation of the cell/material interaction: Concentration (10^7), time contact (20, 60 minutes), adhesion, proliferation, differentiation, liquid suspension (platelet or albumin 4%). Collaboration with UULM, INSERM, EFS, UNIMORE, within WP4.
- Studies performed with INSERM: In vitro tests using mice CSM and MBCP+ to analyse the effect of different culture parameters.
- MBCP+ granules/collagen membranes sent to different REBORNE partners (UULM and INSERM).
- Test of Cells and fluid absorption: Test on the mixing of concentrate bone marrow with MBCP+ granules in low pressure syringe packaging

b) Work carried out by INSERM #1

b.1. Characterization MBCP+

- Physico chemical Analysis on the MBCP+ furnished by BIOMATLANTE.
- Particularly microporosity and distribution of micro, mesopores and macropores have been realized on different batches to determine the reproducibility.
- High resolution SEM and Hg porosimetry have been realized.
- High temperature test have been applied to neutralize micropores effects and *in vitro* and *in vivo* tested are in progress.

b.2. Development of osteoinductive concavities in porous CaP granules scaffold

- Evaluation and characterization of new technologies for elaboration of 3D macroporous rounded granules with high concavities structure.
- First synthesis realized, physico-chemical and 3D structural analysis in progress

b.3. Preparation and characterization of freeze drying suspensions

- Elaboration of mixture of polysaccharidic aqueous hydrogels and MBCP granules
- *In Vitro* tests of reconstitution with biological fluid and PRP

b.4. Physico chemistry of Calcium phosphate bioceramics scaffolds for tissue engineering

- Development of an automatic reactor of 2.5l with control of pH, temperature and agitation.
- Synthesis and characterization of CDA obtained by calcium and phosphate salts decomposition and precipitation:
- Development of optimized process of measurement of global macroporosity and intergranular spaces of granules for MBCP bioceramic by micro CT.

b.5. Fundamental biological properties

- Determination of best ratio for surgical handling of combination of MBCP granules (different sizes) with Blood, PRP, Bone marrow.
- In vivo test in large animals for osteoinductive properties characterization, in progress
- Analysis of implanted MBCP and STEM cells in calvaria rat model of bone implantation.
- In vitro tests of new generation 3D BCP scaffolds, in progress.

b.6. Kinetic of attachment of hMSCs on MBCP+ granules

The kinetic and efficiency of attachment of human mesenchymal stem cells on macroporous biphasic calcium phosphate granules have been determined by INSERM #1 and corroborated by UULM #16 and by UNIMORE #12. It has been shown that about 50 % of ***hMSCs could attach to the surface of MBCP+ granules within 1 hour, a time span that is compatible with surgery***. Increasing the duration of contact time did not significantly increase the efficiency of cell adhesion on the biomaterial. Furthermore, the efficiency of cell adhesion has been shown to relate to the number of cells per ml of medium and cm^3 of MBCP+ granules. Increasing the number of cells resulted in the

increase of cell attachment on the biomaterial in a given volume. ***The optimal dose of cells was determined to be 20 million hMSC per cm^3 (0.5 g) of MBCP+ granules***.

b.7. Proliferation of hMSCs on MBCP+ granules

The MBCP+ biomaterial is biocompatible to support growth of cells. As shown by live and dead assays, cells were alive on the biomaterial. In addition, hMSCs proliferated very well on the MBCP+ granules. Numbers of cells seeded on the MBCP+ granules increased with culture time. Comparison of cell growth on MBCP+ granules and on Glass beads for cell culture indicated similar cell proliferative curves. Human MSCs produced abundant extra cellular matrix, mainly collagen type I. Hybrid complexes of hMSC/MBCP+ granules and ECM have been produced within few days.

b.8. Osteoblastic differentiation of hMSCs on MBCP+ granules

Human MSCs cultured on MBCP+ granules differentiated into osteoblasts even without the addition of soluble osteogenic factors such as dexamethasone, beta-glycerophosphate, ascorbic acid or bone morphogenetic proteins. Osteoblastic genes such as osterix, ALP, Coll I, OCN and BSP were over expressed in culture of hMSCs on MBCP+ granules as compared to culture on plastic. Furthermore, bone proteins were produced by cells in culture on MBCP+ granules as shown by immunohistochemistry corroborating gene expression results by PCR. Spontaneous osteoblastic differentiation of hMSCs on MBCP+ granules was observed without the addition of soluble cytokines. Platelet lysate (PLP) derived from human blood has been shown to enhance both the proliferation and osteoblastic differentiation of hMSCs on the MBCP+ biomaterial. It is therefore possible to avoid xenobiotic substances such as fetal calf serum (FCS) in culture of hMSC for the safety of patients.

b.9. Osteogenicity of hMSC and MBCP+ granules

Human MSCs from bone marrow were cultured in PLP. Twenty million hMSCs were then mixed with 1 cm^3 (0.5 g) of the MBCP+ granules 1-2 mm for 1 hour and implanted in subcutis of nude mice. After 8 weeks, histology revealed that ***well mineralized bone tissue formed ectopically in contact with the MBCP+ granules***. Bone tissue was mainly observed at the periphery of granules nearby vascularization. Therefore, the conditions and the dose of cell to induce bone formation have been determined: 20 million hMSCs expanded in platelet lysate were just mixed for 1 hour with 1 cm^3 of MBCP+ granules and implanted in subcutis of nude mice.

Task 2. Research and development of injectable bone substitutes with osteoinductive properties

a) <u>Work carried out by BIOMATLANTE #3</u>

- Exchange of materials (chitosan and CaP ceramics) between BIOMATLANTE and KITOZYME. First tests (choice of the polymer, sterilisation effect, formulations, etc).
- Contact with Nathalie Chevallier from EFS. Supply of CE marked materials and prototypes for Ortho2 and 3 clinical trial:
  - MBCP-Gel (CE marked)
  - High viscous materials (prototypes, 2 types and 2 ancillaries)
  - MBCP+ in low pressure syringe (used for clinical trials Ortho1 and Maxillo1)

- Analysis and development of suspension Hydrogel/BCP. Optimisation of suspension MBCP Gel, development of high viscous suspension of Hydrogel and MBCP granules, tests on sterilization process, packaging evaluation. Analysis and characterization of US and CE commercial products combining hydrogel and calcium phosphate granules.

b) Work carried out by KITOZYME #8

The objective for KitoZyme in this task is to develop **hydrogels** made of chitosan from vegetal resources. These materials will have to be used as a carrier for autologous and allogenic MSCs injection in patients with early avascular necrosis of the femoral head (second and third clinical trial in orthopaedic surgery-see WP5). The work has been developed in two areas:

i) KitoZyme has prepared a series of hydrogels composed of chitosan using different cross-linking strategies that can be classified into two main categories, i.e. (1) physical/ionic and (2) chemical/covalent cross-linking:

- (1) physical cross-linking: can be obtained by using polyanionic salts (PAS) or anionic macromolecules (AM) as Xlinker
- (2) chemical cross-linking: can be obtained with di-functional polymers (DFP) or with naturally occurring Xlinker (NOX)

Gels have been prepared and characterized for the different properties (gelation time, hardness, stability in contact with culture medium, rheology, pH, osmoloarity,...).

ii) On the other hand, KitoZyme is participating in the development of new **injectable composite bone substitutes** in collaboration with BIOMATLANTE. KitoZyme and BIOMATLANTE have been in contact on September 22 in order to define the steps for the development of an injectable hydrogel composite made of chitosan and granules of CaP to be tested in clinical trials ORTHO2/3. Granules of CaP of two different granulometries will be transferred from BIOMATLANTE to KitoZyme, under MTA. KitoZyme will test the incorporation of the CaP granules into the different hydrogel compositions. In the other side, KitoZyme will transfer to BIOMATLANTE chitosan and chitosan derivatives, in the form of powder, to be mixed with CaP granules and to evaluate the formation of gels after suspension in medium culture and to evaluate the sterilization.

The progress of the work is summarized below.

b.1. Chitosan 2 parts-gel formulation with polyanionic salts (PAS)

b.1.1. Preparation and characterization of hydrogels

Two-parts, thermogelling chitosan gels are prepared by mixing Part A and Part B in a defined vol/vol ratio.
The composition is Part A and Part B is the following:

- Part **A:** chitosan solution in a cc range of 1.25-2% in HAc 0.05M-0.1M.
- Part **B** : aqueous solution of PAS at different cc. Different PAS have been used, refereed as AP, GP and TPP

Part B is added to Part A and the solution is mixed using a Vortex for a few seconds. A gel is formed when the solution is incubated at 37°C. Gelation time, temperature, pH, morphology and osmolarity of the gels have been characterised.

b.1.2. Rheological analysis

The best formulation was further characterized for rheological properties using a rheometer. The rheological analyses showed that gelation of chitosan solutions using PAS-1 as a physical cross-linker occurs within 5-6 min at 20°C and 30 sec at 37°C as determined by rheological measurements. Dilution of the Xlinking part did not influence the gelation time but decrease the gel cohesion. Gels formed at 37°C are more cohesive than the one formed at 20°C that need more time to be formed.

b.1.3. Gel porosity as observed by SEM

Gels were further characterized by scanning electron microscopy, showing a porous structure.

b.1.4. In vitro evaluation

Some series of hydrogels were sent to ESF for further *in vitro* evaluation on contact with stem cells. Cell will be mixed to the gels once formed by addition of Part B to Part A. Cell survival, adhesion and proliferation will be further evaluated in order to determine the gel cytotoxicity and to select the best gel formulation in term of biocompatibility.

b.1.5. Gel injectability

Some series of hydrogels were prepared and sent to Prof. Hernigou (Service d'Orthopédie et Traumatologie- Hôpital Henri Mondor, FR) for testing the injectability of the hydrogels into bone explants (femoral head for osteonecrosis indication).

b.2. Chitosan 2 parts-gel formulation with anionic macromolecule (AM)

Chitosan gels were prepared by mixing 1/3 of chitosan solution to 2/3 of AM solution (Part A) (vol/vol) using ultraturax. Part B, a salt able to precipitate the AM is added to part in a vol/vol ratio of 93/7. A gel is formed spontaneously after addition of part B to part A and mixing at room temperature. Their physic chemical characterization is in course.

b.3. Chitosan hydrogel Xlinked with difunctional polymer –DFP

Chitosan gels were prepared by dissolving 1% chitosan in HAc 1% and adding a di-functional polymer. A gel is formed once the mixture is heated at 60°C. The gelation time is longer (overnight). The characterization of this gel is in course.

b.4. Chitosan hydrogel Xlinked with naturally occurring Xlinker (NOX)

Chitosan gels are prepared by addition of 0.005M of NOX to a solution 1% chitosan in HAC 1%. The gel was formed overnight at room temperature. These gels are much though and with a dark blue color due to the coloration of the Xlinker. Physico chemical characterization is under way.

b.5. Hydrogel/CaP composites

KitoZyme has tested the incorporation of CaP granules provided by BIOMATLANTE. Granules of different size have been tested and at different weight ratio into the hydrogel. Gels Cs-Ammonium Phosphate containing CaP granules with different v/v ratio, i.e. 30%, 20% and 10% v/v have been prepared using granules of different granulometry, i.e. 80-200µm and 40-80µm. The gelation time has been estimated to 15min in presence of the

CaP granules in comparison to 10min without granules. The larger granules (80-200µm) tend to sediment to some extent. The formulation with the smaller granules appears to be the most stable.

During this first year of the project, KitoZyme has successfully prepared different formulations of injectable chitosan hydrogel as well as injectable chitosan/CaP composites. The first screening of chitosan gels will be completed by further characterization, as well as evaluation in contact with cells in collaboration with partners involved in *in vitro testing* in order to indentify the best formulation(s) to be further tested in pre-clinical and clinical trials (ORTHO2/3). The formulations are currently being tested for cell survival and attachment in contact with mesenchymal stem cells and for injectability into femoral head in view of further optimization of the gel and selection of the best candidate to be further evaluated into clinical trials.

c) Work carried out by XPAND #9

Injectable/moldable osteoinductive bone void fillers composed of carboxymethyl cellulose gel (CMC)-with tricalcium phosphate (TCP) granules formulations do not exhibit long shelf-life stability (less than 1 year) because of the fast dissolution kinetic of the TCP granules. To overcome the fast degradation of the osteoinductive granules, XPAND has initiated the preparation of CaP ceramics with higher hydroxyapatite (HA) content in order to reduce the degradation of the CaP granules in contact with hydrogels. Currently, powders with 40, 60 and 80% content of HA have been prepared. The sintering and control of porosity will be further studied during the upcoming period to prepare granular material.

In parallel to this, two well characterized BCP materials are subjected to cell culture to get insight in the osteoinduction mechanism of CaP ceramics. The objective is to investigate the interaction between an osteoinductive surface and macrophages (murine, human) compared to a negative control (non-osteoinductive ceramic). This on-going project involves collaboration with Dr. P. Layrolle (INSERM U957 – LPRO). Once the macrophage culture and screening system have been well established with the positive and negative BCP controls, the newly developed ceramics will be subjected to the same cell culture conditions.

Moreover, in the past 3 months, XPAND has participated in the regulatory submission of the TCP granules. The CE mark was obtained in January 2011. To date, only 1-2mm CaP granules were tested in the treatment of palate cleft defects. The clinical evaluation of smaller particle sizes, eg 500-1000 microns, is recommended to mimic a putty/injectable formulation.

Although granules are acceptable with respect to end user's requirements, XPAND is currently evaluating the regulatory strategy for CE marking of an injectable or putty formulation of the osteoinductive granules for maxillofacial applications.

Task 3. Research and development of osteoinductive, angiogenic, high strength and resorbable composites

a) Work carried out by UPC #10

The main objectives of this first year falling within Task 3 were focused, as stated in Annex I of the Reborne project, on the unsolved challenge of obtaining high mechanical strength for body load bearing applications in combination with rapid resorption calcium phosphate biomaterials. Therefore, the following tasks were carried out or are in course to achieve the above ambitious objectives:

- Research and development of self setting calcium phosphate cements with intrinsic osteoinductive properties and high strength
- Research and development of composites based on calcium phosphates cements or ceramics and bioresorbable polymer nanofibres
- Physico chemical and mechanical characterization of composites

a.1. Development of Biphasic Calcium Phosphate Cements (BCPC) as potential self setting osteoinductive materials.

Biphasic calcium phosphate cements (BCPC) were prepared, consisting after setting of different proportions of Hydroxyapatite and β-TCP. This was achieved by combining different amounts of a reacting phase (α-TCP) and a non-reacting phase (β-TCP). After mixing with water α-TCP hydrolyses to a calcium deficient hydroxyapatite and β-TCP remains untransformed.

$$\alpha\text{-}(Ca_3(PO_4)_2 + \beta\text{-}(Ca_3(PO_4)_2 \rightarrow Ca_9(HPO_4)(PO_4)_5(OH) + \beta\text{-}(Ca_3(PO_4)_2$$

The following steps have been undertaken:

- *Preparation of Biphasic Calcium Phosphate Cements (BCPC) from different weight ratios of the polymorphs (ranging from 100% α-TCP to 20:80% α-TCP:β-TCP)*

Three series of BCPC were prepared with α/β weight ratios of 80:20, 60:40, 20:80. 100% α-TCP cement was used as a control. The BCPC were characterized in terms of the setting properties (cohesion and setting times), phase composition, porosity, specific surface area, microstructure and mechanical properties. Initial and final setting times, as well as cohesion time increased with the higher percentage of the α-TCP phase in the CPC. Increase of powder particle size also increased setting times and cohesion time, which can be related to differences in particle dissolution rates. In some cases, very high percentages (80%) of α-TCP in the biphasic cements limit a perfect cohesion of the paste even after long time. This may be solved by the introduction of certain additives in the BCPC, a point currently under study.

- *Characterization of the set cement*

The phase composition of the different BCPC was evaluated by X-ray diffraction. It was assessed that the α-TCP was transformed to a CDHA during the setting of the cement

and the β-TCP remained untransformed and embedded in the CDHA matrix. Moreover, it was observed that introduction of α-TCP progressively reduced the specific surface area (SSA) in BCPC prepared both from fine or coarse α-TCP powders. BCPC made from fine powders had higher SSA than those made from coarse powders, which is closely related to their microstructure. Mechanical properties being a relevant parameter in biomaterials intended for bone regeneration, compressive strength of the cements was evaluated at different setting times. Increasing α-TCP percentage in the BCPC progressively reduced their mechanical properties. It has been shown that the compressive strength tended to improve with the evolution of the setting reaction and the transformation of α-TCP into calcium deficient hydroxyapatite.

a.2. Research and development of composites based on calcium phosphate cements or ceramics and bioresorbable polymer fibres

Calcium phosphate cement (CPC) composites with bioresorbable Polylactide (PLA) fibres have been prepared by using the α-Tricalcium Phosphate (α-TCP). PLA fibers were obtained from ≈320 µm diameter yarns, which were conveniently cut to lengths allowing optimum introduction and mouldability of the CPC pastes.

Physico chemical and mechanical characterization of composites

PLA fibers of ≈10-15 µm diameter were introduced randomly oriented into the CPCs. Formulation of the CPC-fiber composites was optimized according to different parameters with views on future clinical applications. According to previous works, PLA has low wettability, which may hamper integration in the cements, and thus affect the mechanical properties of the final cements. To avoid it, a plasma treatment was carried out to increase wettability of the fibers. That treatment was effective in increasing wettability of the fibers, resulting also in an effective decrease of free liquid available, which reverted in a decreased setting time in the fiber-containing CPC composites.

Good integration of the PLA fibers in the CPC composites was observed in all cases by SEM. At present the effect of the fibers on the mechanical properties of the cements is being evaluated through 3-point bending and compression tests.

b) **Work carried out by MPG #22**

b.1. Synthesis of Poly(urethane/urea) Capsules and Release of Payload

Studies on the encapsulation efficiency using fluorescence measurements

To determine the permeability of the capsule shell the encapsulation efficiency of the fluorescence dye SR101 at different time periods was measured by fluorescence spectroscopy. This dye absorbs light at 590 nm and emits light at 605 nm. The poly(urethane/urea) nanocapsules were treated with hydrochloric acid or sodium chloride in order to adjust the pH value. The total release of the SR101 from the capsules was calculated from the difference of the fluorescence intensities of the supernatant between the capsules with the dye inside the core redispersed in water and the empty aqueous capsule cores redispersed in SDS-SR101 solution (for 100% release). The percentage of the released dye over the time could then be evaluated. The percentages of the released dye from the capsules prepared with the corresponding monomers after 20 days of certain

pH treatments are demonstrated. Possibly this pH dependency could be used in future for a controlled capsule degradation. The release of the dye out of the capsules is very slow at all pH values, i.e. basic, neutral or acidic. One exception is that the release of the dye out of the capsules synthesized from 1,6-hexanediole and TDI in the presence of P(E/B-*b*-EO) as surfactant is under 25% after 30 days. Therefore it has to be seen that every system is very complex and unique and has to be observed by its own.

Thermal stability of the polymeric capsules

Differential scanning calorimetry was used to study the thermal behavior of synthesized polymeric capsules. The polymeric nanocapsules have a glass transition temperature (Tg) at day 0. Although all obtained glass transition temperatures are in the range of their listed literature values (polyurethane between 0 and 100°C and polyurea between -100 and 60°C. It should be kept in mind that the synthesized capsule's shell consists of a mixture of urea/urethane units. The Tgs of the capsules made from 1,6-diaminohexane and TDI were higher than the observed Tgs from the capsules synthesized from 1,6-hexanediole and TDI. Therefore, it can be assumed that the used surfactants have a major influence on the resulting glass transition temperature.

Characterization of the shell composition by FT-IR

FT-IR spectroscopy measurements were performed to achieve the different ratio values of the capsule polymer conformation. All synthesized capsules consist of a mixture of urea and urethane units. As assumed, after synthesis the percentage of urethane in the capsule's shell prepared with the monomer 1,6-hexanediole and TDI is above 80% independent of the surfactant ((P(E/B-*b*-EO) or Lubrizol®U) used. When 1,6-diaminohexane is used for the polyaddition reaction with TDI the urea formation is favoured with over 75%. In fact, no urethane unit should be detectable in this polymer composition even if the side reactions (TDI with water or surfactant) are considered. Because of the origin of the surfactants which can introduce their IR-active groups in the spectra some urethane band assigned. Therefore the urethane compositions vary with the used surfactant. After 20 days of pH exposure the percentage ratio of urethane units decreases in all polymeric compositions. During this time the reaction of the residual amount of TDI with the OH groups originated from the water takes place. This may lead to the increase of the urea units and therefore the decrease of the urethane to urea ratio.

b.2. Synthesis of Poly-Butylcyanacrylate Capsules using different oils as continuous phase

In the previous part, we had used polyurethane or polyurea as capsule material. As we had used PBCA for another project (performing PCR in confined mini emulsion droplets) and as we saw that PBCA may as well be tolerable in cell cultures, we investigated if we could also make PBCA capsules in order to have a more rapid release.

Characterization of nanocapsules

The average size and the size distribution of the nanocapsules were determined by dynamic light scattering. For morphological observation, transmission electron microscopy (TEM) was carried out.

Synthesis of PBCA capsules using different oils as continuous phase

In an earlier publication of our group Miglyol 812N and different amounts of a surfactant (Span®80, Tween®80 or a mixture of Span®80 and Tween®80) were used as the continuous phase for the formation of PBCA nanocapsules in inverse miniemulsion. This oil is very suitable to prepare PBCA nanocapsules but we needed to improve the stability of the miniemulsion. Three types of oils with different physical properties were chosen. The effect of the oil type on the capsules characteristics was analyzed in terms of size, size distribution (DLS) and morphology (TEM). The obtained average diameter of the capsules was in all samples in the size range of 250 to 320 nm. No precipitation, coagulation or flocculation of the capsules was observed throughout the experiment. The average capsule size in the TEM images is slightly smaller than that measured by DLS, as a result of the drying. In the SEM images it could also be seen that the polymeric shell is quite stable and does not lead to the collapse of the capsules upon drying.
In conclusion, PBCA nanocapsules with an aqueous core were synthesized via anionic interfacial polymerization of n-butylcyanoacrylate at the water/oil miniemulsion droplets. Using various oils as a continuous phase no difference in the final capsules size was observed. The obtained average diameter was in the size range between 250 and 320 nm. The size was approximately the same after redispersion of the obtained capsules in the aqueous medium containing ionic surfactant (270-290 nm), whereas the redispersion in the non-ionic polymeric surfactant Lutensol AT50 results in slightly bigger capsules with a diameter of 330 nm.

3.2.1.2 Significant results of WP1 during the period

Task 1.1

- The biomaterial to be used for the ORTHO1 and MAXILLO1 clinical trials has been selected to be MBCP+ granules of 1-2 mm. This biomaterial is CE marked and FDA 510(k) approved.
- A packaging device (syringe) has been designed for allowing association of CaP ceramics granules with cells.
- CaP granules have been physicochemically and biologically characterized with views on supporting hMSCs attachment, growth and osteoblastic differentiation.
- High numbers of hMSCs attached within 1 hour on the biomaterial. This contact time is compatible with a surgery.
- hMSC proliferated very well on the biomaterial, produced abundant extracellular matrix and differentiated into osteoblasts even without adding osteogenic factors in the culture medium.
- The osteogenic properties of CaP ceramics and cell constructs have been evaluated in small animal models with various cell sources, at different doses, in osteogenic conditions.
- The dose of hMSCs was determined to be 20 million per cm^3 of MBCP+ granules in order to induce newly formed bone tissue *in vivo*. In the clinical trials, the dose of cells will be 100 million for 5 cm^3 of MBCP+ granules.

Task 1.2

- Different formulations of injectable chitosan hydrogels as well as injectable chitosan/CaP composites have been prepared (partners #3 and 8). (ORTHO2/3 clinical trials).

- Different formulations of putty like substitutes based on TCP granules and hydrogels have been developed (MAXILLO2 clinical trial). The CE mark for the TCP granules was obtained in January 2011.
- Further characterization, as well as evaluation in contact with cells in collaboration with partners involved in *in vitro* testing in order to indentify the best formulation(s) must be further tested in pre-clinical and clinical trials

Task 1.3
- Self setting biphasic calcium phosphate cements have been developed and their optimisation is in course.
- Composites based on calcium phosphates cements and bioresorbable polylactic acid fibres have been prepared.
- Synthesis of Poly(urethane/urea) and Poly-Butylcyanacrylate nanocapsules for bioactive molecules and fluorescent dye release has been optimized.

3.2.1.3 Main deviations from Annex I

No significant deviations have been detected in WP1.

3.2.1.4 Use of resources of WP1

Participant number	Participant short name	Staff effort (men-month)		Cost	
		Planned	Actual	Planned	Actual
1	**INSERM**	17,42	1,51	142 498 €	28 275 €
3	**BIOMATLANTE**	27,36	13,35	171 000 €	99 724 €
8	**KITO**	15,00	8,41	118 464 €	76 698 €
9	**XPAND**	20,40	24,00	140 640 €	176 363 €
10	**UPC**	11,70	15,00	102 112 €	151 056 €
22	**MPG**	10,80	31,50	137 880 €	186 577 €
TOTAL		**102,68**	**93,77**	**812 594 €**	**718 694 €**

The main deviations between actual and planned person months are related to a wrong effort planning at the beginning of the project for RTD of new biomaterials and to a reallocation of the tasks repartition between the participants. BIOMATLANTE's biomaterials were almost ready at the beginning of the project (MBCP+ granules are CE marked) and main RTD activities have been conducted for *in vitro* and *in vivo* testing of cells/biomaterial combinations in relation to WP4.

3.2.2 WP2– Cell Production

3.2.2.1 Summary of progress towards objectives and details for each task of WP2 during the period

The main objective for the first year of the work of the WP2 was to implement GMP protocols for the culture of bone marrow mesenchymal stromal cells (MSC), adipose-derived stromal cells (ASC) and fetal blood mesenchymal stromal cells (FB-MSC). The work was based on the known how of the participating teams. One main goal to set-up each GMP production culture protocol was to replace, as far as it is possible, the xenogenic medium additive (mainly fetal calf serum) by a human substitute based on platelets blood products. Three items had to be delivered during the first year:

- D2.1 Definition of the preparation of platelet growth factor enriched plasma (PGFEP) a the FCS substitute.
- D2.2 Standard operating procedures for the GMP culture of MSC and ASC.
- D2.3 Standard operating procedure for the GMP culture of FB-MSC.

The fourth item was to produce the cells for the first two clinical trials. It has been postponed to month 15 to be on line with the beginning of the clinical trials.

For the first deliverable, two partners (UULM#16 and EFS#2) had shared they experience and evaluate the more convenient protocol to produce large amount of the platelet blood derivative PGFEP. Based on this work, the partners have compared culture protocols (deliverable 2.2) in order to define the best compromise. The criteria were defined as medium consumption, cell growth efficiency, length of the culture, personnel expenses.

All the experiments performed allowed us to choose the more convenient GMP cell culture protocol for the first two clinical trials.

3.2.2.2 Significant results of WP2 during the period

Comparison of production methods for platelet blood derivative was conducted. The UULM method use pools of platelets prepared from whole blood while the EFS method use platelets preparation from aphaeresis. Although a little bit less efficient (see figure 1), the UULM method to produce PGFEP was chosen to culture MSC because, the product is already validated by the German regulatory authorities and, the partner could produce large amounts of this medium supplement per batch. Therefore, this high production yield will reduce the variability in the preparation of the complete medium for producing clinical lots of hMSCs. Consequently, each partner will use the same batch of PGFEP for the production of clinical lots of hMSCs, thus reducing variability between production centres.

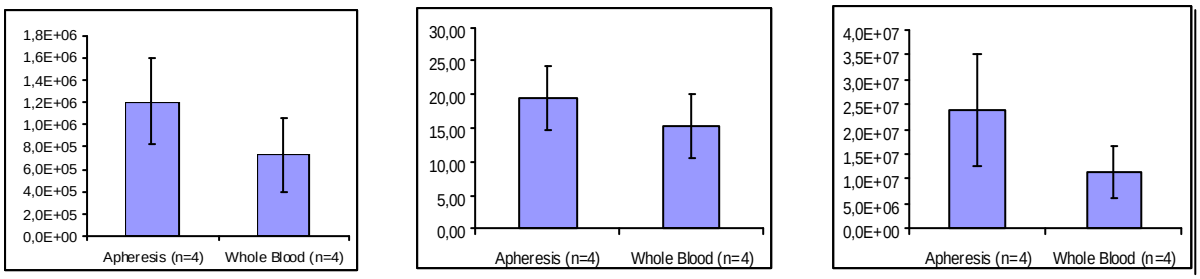


Figure 1. Comparison of protocols for producing platelet blood derivative PGFEP

The main participants to the evaluation of the culture process for MSC were UULM and EFS. The Cell Factory partner in Milan and the Madrid partner participated only in one experiment each. Four culture protocols were compared according to the discussion between partners. All procedures are based on two step protocols, as following:

1) First period of culture of 10 days with a medium containing 5% of PGFEP, then a second period of 5 days in a medium + 8% of PGFEP.
2) First period of culture of 14 days with a medium containing 5% of PGFEP, then a second period of 7 days in a medium + 8% of PGFEP.
3) First period of culture of 10 days with a medium containing 10% of PGFEP, then a second period of 5 days in a medium + 10% of PGFEP.
4) First period of culture of 14 days with a medium containing 10% of PGFEP, then a second period of 7 days in a medium + 10% of PGFEP.

These protocols were compared and the results are shown in the table below. The main finding was that the more significant factor that defines the number of cells obtained after the complete process was the number of days of culture. Another important parameter was the quantity of PGFEP needed for production of a clinical batch. Thus, the protocols using the lowest amount of PGFEP were selected. This procedure leads to save at least 200 ml of PGFEP per patient thus an expected sparing of 6 liters of PGFEP for each of the first 2 clinical trials. Furthermore, the shortest protocol gave results not significantly lower than the longest. Therefore, it was decided to choose the protocol n°1 in order to provide the cells to the patient rapidly.

By using the GMP protocols tested, we were able to produce a mean of at least $5x10^7$ MSC/Cellstack™ 2 layers, in 15 days for the shortest and 21 days for the longest.

The phenotype of the cells was consistent with MSC. The cells had been provided to the partners of WP4 to perform potency assays.

According to the results we obtained, we were able to evaluate the number of Cellstack™ 2 layers to be utilized during the 2 phases of the culture: no more than 4 for the 2 phases of culture to be sure to produce more than 10^8 MSC.

Experiment code	5% - 8% 15 days	5% - 8% 21 days	10% 15 days	10% 21 days
	N=6	N=9	N=6	N=10
	Bone marrow			
Cell viability	94,8% ± 1,8%	95,6% ± 1,9%	95,3% ± 2,1%	96,1% ± 1,9%
CFU-F frequency (for 10^6 BM cells)	83,2 ± 33,6	69,4 ± 36,0	85,3 ± 41,9	78,8 ± 40,1
	Primary culture			
Number of days	10 ± 0,0	14 ± 0,5	10 ± 0,0	14 ± 0,5
Cells/cm²	15 989 ± 8 051	32 508 ± 22 335	12 362 ± 6 937	41 516 ± 31 247
Cells/1CS 2L	2,03E+7 ± 1,02E+7	4,13E+7 ± 2,84E+7	1,57E+7 ± 8,81E+6	5,27E+7 ± 3,97E+7
Viability	97,3% ± 1,5%	96,2% ± 4,6%	94,8% ± 7,8%	94,2% ± 6,2%
Expansion factor	4 445,4 ± 2 821,6	11 097,3 ± 8 967,0	3 094,2 ± 1 861,1	12 493,1 ± 10 880,1
Number of Population doublings	11,9 ± 0,8	13,0 ± 1,2	11,4 ± 0,9	13,2 ± 1,1
Doubling time	20,2 ± 1,4	26,0 ± 2,5	21,2 ± 1,6	25,6 ± 2,3
CFU-F frequency (for 200 cells)	37,8 ± 27,7	52,8 ± 30,4	40,6 ± 23,8	42,9 ± 23,3
	1st passage culture			
Number of days	5 ± 0,0	7 ± 0,0	5 ± 0,0	7 ± 0,9
Cells/cm²	41 188 ± 19 174	52 260 ± 28 383	41 446 ± 18 163	48 519 ± 27 456
Cells/CS 2L	5,23E+7 ± 2,44E+7	6,64E+7 ± 3,60E+7	5,26E+7 ± 2,31E+7	6,16E+7 ± 3,49E+7
Viability	97,1% ± 1,8%	97,9% ± 1,1%	94,7% ± 2,7%	94,0% ± 5,7%
Expansion factor (numeration)	10,3 ± 4,8	12,9 ± 7,6	10,4 ± 4,5	11,7 ± 7,1

3.2.2.3 Main deviations from Annex I

The main deviation in the work of WP2 was a delay to provide the deliverable 2.2. The reason was the length of the tests we had to perform to have a real comparison of the 4 culture protocols. However, this has a little impact on the work of the consortium.

3.2.2.4 Use of resources of WP2

Participant number	Participant short name	Staff effort (men-month)		Cost	
		Planned	Actual	Planned	Actual
2	**EFS**	12,00	3,93	151 242 €	91 893 €
5	**POLICLINICO**	11,52	18,00	55 014 €	85 473 €
16	**UULM**	5,76	8,86	78 950 €	52 369 €
17	**UNIVR**	1,68	2,06	16 539 €	67 088 €
TOTAL		**30,96**	**32,85**	**301 745 €**	**296 822 €**

The main deviations between actual and planned person months are related to a reallocation of the tasks repartition between the participants. Furthermore, activities and cost were mainly related to the validation of protocols for GMP produced cells. When the production of batches of hMSC for clinical trials will start, a significant increase in allocation of resources and cost is expected

3.2.3 WP3 – Quality controls

3.2.3.1 Summary of progress towards objectives and details for each task of WP3 during the period

The WP3 of REBORNE has the following objectives:

Primary

1. Establish quality controls for MSC in combination with suitable bioscaffolds for bone repair.

Specific

1. Establish safety controls including: genetic stability and immuno-reactivity for cryopreserved/thawed MSC;
2. Establish rapid potency assays including: immunophenotypic and gene profile cytokine secretion assays.

WP3 focuses on the quality control issues raised by the use of bio-compatible materials and mesenchymal stem cells (MSC) as part of bone regeneration approach.

The WP3 involves 6 different tasks.
Task 1. Quality control on the genotypic stability of BM, AT, CB MSC
Task 2.Quality control on the functionality of BM, AT, CB MSC for bone regeneration
Task 3. Quality control on the phenotypic profile of BM, AT, CB MSC
Task 4. Quality control on immunosuppressive properties of BM, AT and CB MSC
Task 5. Quality on MSC-biomaterials combination
Task 6. Testing refinements

In the first year of the project, members of WP3 have been involved mostly in tasks 1 and 3. Tasks 2, 4 and 5 were started as well and the initial results of these tasks are also involved in this report.

Task 1. Quality control on the genotypic stability of BM, AT, CB MSC

In this first year of the project, partner #5 POLICLINICO and #17 UNIVR have been involved in the standardization of the methods for MSC karyotyping, expression analysis of the main genes involved in cell proliferation (p21, p53, c-myc, hTERT) and telomerase activity. Due to the lack of gold standard methodologies for these analysis, validation of the employed assays followed the guidelines “Note for guidance on validation of analytical procedures: text and methodology” [CPMP/ICH/381/95-ICH Q2 (R1)] and European Good Manufacturing Procedures, Chapter 6, when technical and statistical parameters were applicable (i.e. specificity, sensitivity, robustness, reliability). Five different BM MSC preparations were used: 3 MSC expansion procedures were carried out starting from BM samples of healthy donors according to “in house” expansion protocol in partner #17 UNIVR facility and 2 batches of clinical-grade MSC, following the GMP procedures selected for ORTHO#1 trial (see D2.2) in partner #5 POLICLINICO facility. Partner #17 UNIVR performed MSC expansion in the presence of FBS for three passages (p3-MSC) over 30 days. Partner #5 POLICLINICO followed the GMP procedures selected in WP2.

Karyotyping was carried out on MSC collected at the end of the production, according to the technical procedures employed in the prenatal diagnosis (in situ methods). For the gene expression analysis, real time reverse-transcribed polymerase chain reaction was carried out after RNA extraction (Rneasy kit, QIAGEN), cDNA synthesis (High-Capacity cDNA Archive kit, Applied Biosystems) and amplification (TaqMan Gene Expression assays and TaqMan Universal PCR Master Mix, Applied Biosystems). Before starting the validation, the Real Time PCR System was adequately calibrated by using a Spectral Calibration Kit (Applied Biosystems 7300). Several housekeeping genes were screened in MSC collected at the first and third passage (p1- and p3-MSC), by employing the TaqMan Express Endogeneous Control Plate (Applied Biosystems), to detect a normalizer whose expression was not modified by proliferation kinetic or senescence. Each gene expression level was normalized to glyceraldehyde-3-phosphate-dehydrogenase (GAPDH) or beta-2-microglobulin (B2M) levels and compared to that of MSC collected at the first passage (p1-MSC).

Partner #5 POLICLINICO validated different methods for the evaluation of telomerase activity. In particular, for BM a QRT PCR using SYBR Green (Quantitative Telomerase Detection kit, QTD Kit, Allied Biotech Inc.) was tested. This method is a sensitive assay based on a one step PCR reaction. In the first part of the reaction, the active telomerase from lysed cells/tissues sample adds a varied number of telomeric repeats (TTAGGG) onto the 3' end of the substrate oligonucleotide. These extension products are then amplified by polymerase chain reaction (PCR). Generated PCR products are directly detected by measuring the increase in fluorescence caused by binding of SYBR Green to double-strand DNA. A control template for quantitative analysis of the samples was also used. The 2 batches of GMP-grade BM MSC had both low telomerase activity as compared to HELA cells used as positive control. For CB Telomerase activity (TRAPeze ELISA kit, Millipore) was tested to know if they had a propensity for spontaneous transformation. The results demonstrated that telomerase activity was lower than that obtained with HELA cells (22.92nm), used as control.

All together these results support the genetic stability of BM-MSC produced under GMP conditions. The same approaches are now followed to test also GMP-produced AT-MSC.

Task 2.Quality control on the functionality of BM, AT, CB MSC for bone regeneration

Partner #5 UNIVR quantitatively evaluated the expression the AOC markers in CB and BM MSCs cultured in differentiation conditions and compared them with MSC cultured in basal medium (without differentiation). For osteogenic differentiation CB-MSCs and BM MSC were grown for 2-3 weeks with MSC Osteogenic Medium (Cambrex) replaced every 3-4 days. Calcium deposits were stained with Alizarin Red (Sigma). For QRT PCR osteonectin and ALP were measured. Osteonectin is a glycoprotein secreted by osteoblasts during bone formation, initiating mineralization and promoting mineral crystal formation. After osteogenic induction, osteonectin and ALP expression was increased. Other functional controls have been performed in Task 5 by evaluating the combination of BM MSC and biomaterials.

Task 3. Quality control on the phenotypic profile of BM, AT, CB MSC

In cooperation with WP2 (partner #2 EFS) partner #16 POLICLINICO modified the already established large scale, GMP-grade expansion system of BM-MSC. The single-step system was replaced by a two-step system. In this task of WP3 partner #16 POLICLINICO studied whether the various modifications have an impact on the phenotype of MSC.

The modifications of the culture procedure did not change the expression of markers which have been established as standard to describe the phenotype of ex-vivo expanded MSC. Extended phenotyping of cells from the two-step system (including chemokine receptors, integrins and markers of early MSC) have also been performed, showing a modulation of integrin expression during passages.

Based on these data, a single step protocol has been chosen for the clinical trial and partner #5 set up a general frame for the quality controls to be implemented during the validation process and the clinical production, which is now available. Also for CB production, extended phenotype screening was performed in order to define the controls on the final product, with particular regards to cell count (manually vs automatic device); evaluation of populations' doublings; flow cytometry and CFU-F.

Task 4. Quality control on immunosuppressive properties of BM, AT and CB MSC

One of the objective of REBORNE is to standardize the experimental methods to assess the immune modulatory properties of MSC obtained from bone marrow (BM), adipose tissue (AT) and cord blood (CB) for clinical use. The effect of interaction with MSC on different immune effector cells (T, B, NK cells) was assessed in terms of inhibition of proliferation and cytotoxicity in response to non-specific stimuli:

Different experimental conditions were compared, as well as the effects of "resting" and "inflamed" MSC. The first sets of experiments were carried out by using BM-derived MSC. Proliferation rate of immune effector cells following interaction with MSC was measured by applying the flow cytometric approach based on CFDA-SE reagent (Invitrogen), according to manufacturer's protocol. Cytotoxicity activity of NK cells towards K562 cell line and MSC (to test MSC immunogenicity) was assessed Inhibition assays by using specific inhibitors (L-1MT, L-NMMA, SnPP, NS-398, anti-IFNγ mAb) to revert the immunomodulatory effect of MSC were also carried out.

All these methods were capable of quantifying in a reproducible manner the MSC-mediated inhibition of T, B and NK cell proliferation and NK cytotoxicity, as well as the resting MSC-mediated support of B cell proliferation. Different results were obtained with resting or inflamed MSC, the latter displaying a more powerful effect. The use of single or multiple specific inhibitors reverted MSC-mediated immune modulation partially or almost completely, respectively. At present, these methods are applied for the characterization of MSC of adipose tissue and cord blood origin: preliminary results are similar to those obtained with BM-derived MSC (further experiments are in progress).

Task 5. Quality on MSC-biomaterials combination

This part was done by Partner #16 UULM in co-operation with WP1 and WP2. In order to develop *in vitro* assays that will predict the seeding efficiency of MSC on different biomaterials, MSC have been co-cultured together with different biomaterials proposed in WP1. In preliminary experiments, we examined the interaction of BM-MSC with MBCP+, i.e. the biomaterial which will be used in the first clinical trials ORTHO1 and MAXILLO1. MBCP+ was provided by partner #3 BIOMATLANTE. BM-MSC were produced according the standardized protocols in WP2. In order to establish the optimal conditions for loading of MSC on the MBCP+ particles, we tested:

- various methods for conditioning of MBCP+ granules prior to addition of BM-MSC
- various periods of incubation of MBCP+ granules with BM-MSC
- incubation of increasing numbers of BM-MSC with MBCP+ granules
- adhesion of MSC on MBCP+ under agitation and for prolonged periods.

Number of MSC on / in the MBCP+ granules were quantified by an LDH test. Interaction also was visualised by raster electron microscopy (REM). It was shown that pre treatment of MBCP+ with PBS is necessary for optimal cell adhesion. Other pre treatments (coating with human platelet lysate or fetal calf serum) did not significantly increase the number of attached cells.

About half maximal adhesion of BM-MSC to MBCP+ cells was achieved already after an incubation of 30 minutes. Maximal adhesion was reached after 6 hours. After short periods of incubation (<= 3 hours) MSC appeared as round cells. After prolonged periods of incubation they showed the typical morphological appearance of MSC with long protrusions. In further experiments we studied whether the overall number of BM-MSC on MBCP+ granules can be increased by proliferation of the MSC on the MBCP+ granules. BM-MSC were allowed to attach to MBCP+. Then, the MBCP+ granules were separated from unbound BM-MSC and proliferation of the MSC population which had attached to MBCP+ was measured up to 168 hours. If MBCP+ granules were incubated with low cell numbers (i.e. $1x10^6$ BM-MSC per cm^3 MBCP+) the MSC proliferated on the MBCP+ granules and increased substantially (about by factor 3) until day 7. However, if larger MSC numbers (i.e. 5 to 10 $x10^6$ BM-MSC per cm^3 MBCP+) were incubated only slight proliferation was observed within the first 24 hours (increase by about 25-30%). Thereafter the number of MSC on the MBCP+ granules remained stable.

In the setting of the clinical trials, the MBCP+ granules will undergo substantial mechanical agitation after incubation with the MSC. Therefore, we allowed attachment of BM-MSC to the MBCP+ granules for only 30 minutes and studied whether the MSC are detached from the granules by movement of the syringe with the MSC-coated MBCP+ on a sample rotating device for various time periods. After 30 minutes of rotation the number of MSC still on the MBCP+ granules were identical to the control which has not been moved.

Overall these results suggested that a large number of BM-MSC can be loaded in a short period of incubation on MBCP+ granules which had been pre treated with PBS. Prolonged incubation did not significantly increase the overall number of MSC on the granules if initially large MSC numbers are used (5-$10x10^6$ BM-MSC per cm^3 MBCP+). The adhesion of MSC to granules is sufficiently strong to sustain mechanical agitation that may occur

during surgical handling or transportation between GMP production facility and the operating theatre.

In summary, hMSCs attached very well on the MBCP+ biomaterial within a short contact time of 1 h that is compatible with surgery.

3.2.3.2 Significant results of WP3 during the period

The WP3 of REBORNE is providing the following significant results during the first reporting period:

- The definition of SOP for MSC production in co-operation with WP2
- Indications to be followed to perform the validation studies in order to collect all the information required to set up appropriate quality controls
- A set of validated tests to be applied on MSC to be used in the clinical trial

All these significant results of WP3 have also been included in the completed deliverables which have been up-loaded on the REBORNE website:

- Deliverable 3.1: Validated protocols for QC on the genotypic stability and phenotypic profile of BM and AT
- Deliverable 3.2: Validated protocols for QC on the genotypic stability and phenotypic profile of CB MSC.

3.2.3.3 Main deviations from Annex I

All the critical objectives of WP3 have been reached.

Tasks 1, 2, 3 and 4 within this WP will be extended also to AT MSC when the AT MSC production system will be fixed in WP2.

The quality controls are related to GMP production of cells. As the standardization and harmonization of protocols between partners has required extensive work, the quality controls could not be properly designed and carried on. In this context, the delay must be considered as physiologic in the start-up of such a multidisciplinary project. The optimization of the exchange of information made in the first year will improve the speed of the project in the next year.

3.2.3.4 Use of resources of WP3

Participant number	Participant short name	Staff effort (men-month)		Cost	
		Planned	Actual	Planned	Actual
2	**EFS**	1,50	5,80	20 712 €	39 967 €
5	**POLICLINICO**	21,60	16,00	106 920 €	61 741 €
16	**UULM**	7,20	11,19	246 720 €	30 658 €
17	**UNIVR**	3,60	0,88	34 456 €	8 647 €
TOTAL		**33,90**	**33,87**	**408 808 €**	**141 013 €**

The main deviations between actual and planned person months are due to a reallocation of the tasks repartition between the beneficiaries; UULM's actual cost gap with the planned cost is due to the fact that UULM is in charge of the quality control which has not started yet since the production has not started too.

3.2.4 WP4 – Functional controls

3.2.4.1 Summary of progress towards objectives and details for each task of WP4 during the period

The WP4 of REBORNE has the following objectives:

1. To provide standardized and novel potency assays combining human mesenchymal stem cells (MSC) and biomaterials to be translated into GMP settings of REBORNE

2. To standardize optimal *in vitro* culture conditions capable to rescue and maintain selected human and animal MSC with robust osteogenic potential when combined with biomaterials

3. To establish biomaterial and MSC combinations focusing on both angiogeneic and osteogenetic potentials to obtain a stronger bone regeneration

4. To explore, *in vitro* and *in vivo*, the impact of immune system on matched and mismatched, differentiated and undifferentiated MSC. The use of immunosuppressive drugs will be additionally assessed considering their influence on bone differentiation

5. To combine biomaterials with optimal source/s of MSC, as single entity or in associations, for an optimal bone regeneration in animal models mimicking selected human diseases

Therefore, WP4 is acting as R&D part of the project dealing with functional controls linked on one side with the development and use of biomaterials (WP-1) and on the other with

the GMP-validation (WP-3) and clinical parts (WP-5 and WP-6) with respect of ethical issues (WP-7). WP4 is providing novel insights for clinical developments of the project to improve bone regeneration capacities of selected cell populations in combination with biomaterials.

The WP4 involves 6 different tasks:

Task 1. Establish improved potency assays for selected GMP-manufactured mesenchymal progenitors (MP) with biomaterials

Task 2. Unification of animal MP culture conditions

Task 3. Explore osteogenic potentials of native human MP in biomaterial combinations

Task 4. Combining angiogenesis and osteogenesis for an improved bone regeneration

Task 5. Impact of immunology and bone regeneration: providing insights for off-the-shelf MP

Task 6. Mimicking challenging clinical trials of bone regeneration with animal models

In these 12 months of the project, the Consortium members of WP4 have been deeply involved in the development and, for selected cases, in the completion of tasks 1, 2, 4, 5. Tasks 3 and 6 were started as well but they are just briefly mentioned in this report since their completion is foreseen in a later stage of the project.

Task 1. Establish improved potency assays for selected GMP-manufactured MP with biomaterials

In this task, we verified if MSC from bone marrow and adipose tissue (namely mesenchymal progenitors MP) isolated and expanded in the GMP facilities were capable of efficient bone differentiation potentials. Potency assays were performed *in vitro* and *in vivo*.

It is known that bone differentiation potential is generally tested after 2 or even 3 weeks. This time corresponds to potency assays in which MSC are induced to generate mineralized matrix with the introduction of bone growth factors and sources of calcium phosphate. This test has two main disadvantages: (a) to provide only qualitative measurements of mineralized matrix by cytochemistry and microscopical observation (b) to be a long *in vitro* assay hard to be considered as a routine based release criteria. In addition, biomaterials and MSC combined potency assays have been marginally considered.

This task improved this current state of the art and, by using spectrophotometric analyses of MSC mineralization potential, we first provided quantitative assessment of the bone differentiation of MSC. Studies were performed in standard 2D culture conditions with

MSC from adipose tissue and bone marrow along with biomaterial combinations. While the first provided very robust results, the latter will be standardized for each of the biomaterials and cell combinations included in the study.

This approach was also validated by matching these data with molecular analyses derived from real-time PCR testing several (8) known osteogenic-related genes. Also two additional novel genes possibly predictive of a bone regeneration potential based on MSC were tested and validated.

We also compared two distinct bone differentiation approaches. One based on BMP-2 and the second on BMP-4. From the obtained results, we can certainly say that GMP-produced MSC by a culture media based on platelets lysates are capable to efficiently and rapidly differentiate in osteogenic cells in both settings. For detailed results see below and in the Deliverable 4.1.

In addition, we wanted to reduce MSC differentiation time for faster bone potency assay to be then introduced as potency assay in the context of the GMP facility (WP-3). The obtained data indicate that after 7 days is possible to obtain a valid bone differentiation dramatically reducing the duration of the potency assay. The further step will be to further reduce this time and standardize a potency assay lasting 48-72 h. The same test has been tested on MSC and biomaterial combinations (in three dimensional cultures). Few technical aspects delayed this part of the project but we have preliminary data (see Deliverable 4.1) and we aim to consolidate those within the month 16th from the beginning of the project.

Having standardized bone differentiation assays, FACS analyses are on-going to assess the integrins expression as parameter to be tested for a MSC-mediated bone repair mediated by biomaterials.
The great part of the work of this year was to standardized bone differentiation assays based on GMP produced MSC. Having done that by two different approaches, we have been recently introducing more sensitive molecular analyses of MSC differentiation based on array techniques testing a wider court of genes related with osteogenic differentiation. Also, the expression on microRNA has also being considered at the different stages of osteoblastic differentiation, providing a more precise signature of differentiation. All these studies will be completed in the current calendar year. The final objective of this approach is to generate fingerprints of bone differentiation considering either marrow or adipose derived MSC. Array studies on the selected MSC are performed in a time course to test this/these early signature/s of bone commitment.

These data will be correlated with the previously mentioned assays and transferred into WP3 for their introduction as QC for product release in the next clinical trials.

Another more basic aspect developed in the WP4 is a gene therapy approach where, by introducing genes or miRNA identified in this first part of task 4.1, we could improve osteogenesis by controlled expression of key gene transcripts able to trigger a more stable bone differentiation. This aspect is just started since the first set of experiments to identify genes able to trigger a more solid bone differentiation has been just completed.

In parallel with *in vitro* studies, *in vivo* experiments in nude mice were performed by INSERM #1 in order to test the bone regenerative potential of MSC and MBCP

biomaterial. Different cell doses of the MSC (mainly from marrow) along with the selected biomaterials (in particular MBCP+) were implanted in ectopic subcutanous sites into NOD/SCID mice for 8 weeks. Histology revealed *in vivo* potency of hMSC/MBCP+ combinations with de novo formation of mature and well mineralized bone tissue in contact with the biomaterial. These findings suggested that MBCP+ granules are a valid biomaterial for the clinical studies and are associated with a bone mineralization (by histomorphometry) when combined with GMP-produced MSC. Complex histological tests are also being implemented and explants have been analyzed by µCT, immunochemistry (Coll I, ALP, BSP, OCN, BMP2, CD31, von willebrand factor).

We have shown that freshly harvested hMSC seeded on MBCP+ granules for 1 h were able to attach on the biomaterial with high efficiency. When implanted in subcutis of nude mice for 8 weeks, ectopic bone formation was observed mainly at the periphery of implants and at the vicinity of vascularization. Bone appeared well mineralized, lamellar with osteocytes and in contact to the surface of biomaterial. It was also shown that the addition of osteogenic factors such as dexamethasone, beta-glycerophosphate, ascorbic acid or bone morphognetic proteins was not necessary to induce *de novo* bone. Culturing cells onto biomaterial prior to implantation is not a prerequisite for ectopic bone formation as well. The quantity of ectopic bone seems only dependent to the number of seeded cells to the quantity or surface of biomaterial. Given the large surface area of biomaterial (eg. 300 cm^2/g for MBCP+ granules of 1-2 mm) and the number of hMSC at confluence (50,000 cells/cm^2) the dose of cells to be seeded on the biomaterial should be 15 million per gram of biomaterial at least. We have found that the dose of cells to induce ectopic bone was 20 million hMSC per cm^3 of biomaterial. This dose of cells is compatible to the production yield of GMP facilities as determined in WP2. For the safety of patients, no xenogenic factors such as fetal calf serum have been used during the expansion of hMSCs. Instead, platelet derivative from human blood was used providing a excellent media for cell proliferation and osteogenic differentiation of hMSCs.

Task 2. Unification of animal MP culture conditions.

Since several partners are developing pre-clinical models of bone regeneration (Tasks 3, 5 and 6), this task is providing to REBORNE standardized methods of MSC isolation and expansion. Where possible, immunophenotypical analyses were introduced. Also *in vitro* potency assays, developed within task 4.1, were introduced to validate the osteogenic potential of MSC.

In this task, we were able to standardize culture conditions for MSC isolated from marrow and adipose rabbit tissues. While the latter were very successfully performed, the first (MSC from marrow) required lots of standardization since the culture media initially introduced where inadequate to determine a relevant cell expansion. Nevertheless, at the end of the first year we can certainly say that we were able to isolate, characterize and expand MSC from rabbit to be used in the pre-clinical phase. In addition, standardized culture conditions for sheep MSC isolated from bone marrow and standardize culture conditions for mini-pig marrow MSC were successfully implemented. In particular for mini-pig we were able to isolate and expand MSC from mini-pig humeral bone marrow showing that the frequencies of mini-pig BM CFU-F are equivalent to human BM CFU-F. In addition, we uncover that mini-pig MSC differentiated correctly in adipocytes and also in osteocytes. This latter appeared more difficult and required major efforts. Nevertheless,

thanks to the modulation of BMP-2 doses, just like for human MSC, we were able to obtain bone differentiation. In selected experiments, mini pig platelets (mpPL), as *in vitro* culture supplements, were introduced and we have been showing that mpPL are able to support MSC expansion as well as FBS just like we have previously show for human PL (Chevallier et al. Biomaterials 2010). Most interestingly, mpPL induce the expression of some osteoblastic gene: like BSP, osteocalcin and osteopontin. Protocols were distributed among the REBORNE partners involved in the pre-clinical studies. For detailed results see below and in the Deliverable 4.4.

Task 4. Combining angiogenesis and osteogenesis for an improved bone regeneration

This task has the purpose to establish novel strategies of bone regeneration based on combinations of osteogenesis and angiogenesis applied to biomaterials. It is known that physiologically bone formation is multistep process in which vessels formation, chondrogenic proliferation and bone replacement are fundamental events. It is also known that inappropriate neoangiogenesis is considered to be a crucial factor in failed bone formation and remodeling. In this challenging task we introduced *in vitro* culture conditions of different MSC combination (from marrow, adipose tissue) aiming to an optimal combination of endothelial and bone differentiations. Vasculogenic growth factors (VEGF, IGF) were introduced and lineage specific markers were assessed by flow-cytometry and RT-PCR.
Very interestingly, MSC expansion within a pro-angiogenic medium (EGM medium) allowed maintaining a pericytic phenotype and function. In addition, this perivascular phenotype showed to be associated with a more immature state and tissue regeneration capacities. Studies were performed *in vivo* and in combination with biomaterial (MBCP+) *in vivo*. For more detailed results see below and in the Deliverable 4.7.

Task 5. Impact of immunology and bone regeneration: providing insights for off-the-shelf MP

Several data suggest that MSC transplantation may be associated to specific immune privilege of transplanted cells. Thus, this task has the main goal to clarify the relationship between immune system and bone differentiating MSC to allow the introduction of biomaterial loaded with mismatched allogeneic MSC into clinics and/or to associate specific immunomodulatory regimens to be applied for late clinical trials in REBORNE. Two main approaches were established in the first year of REBORNE, one *in vitro* and the other, more complex, *in vivo*.

First, we studied the impact of immune cells versus the different sources of MSC included in the proposal The precise mechanisms of *in vitro* immunosuppression and its fine regulation by environmental factors have been here assessed considering the origin of MSC (species, culture conditions), their differentiation status (immature MSC, committed MSC and mature osteoblasts) and by readout systems (responder cell type, activation system, co-culture duration).

This part of the project is also the direct consequence of the Task 4 of the WP3 (Quality Controls on immunosuppressive properties of BM, AT and CB MSC). In WP3 the partners

involved in the immunological aspects of Reborne have carried out several experiments to standardize the experimental methods to assess MSC immunomodulatory properties of MSC *ex-vivo* expanded from bone marrow (BM), adipose tissue (AT) and cord blood (CB) for clinical use. The effect of interaction of different immune effector cells (T, B, NK cells) with MSC was assessed in terms of inhibition of proliferation and cytotoxicity in response to non-specific stimuli (see also WP3 annual report).

In addition, to the in vitro part, REBORNE foresees to establish a mouse model with humanized immune system such as the NOD/SCID–IL-2γc knockout. This model will address whether human HLA-mismatched MSC are rejected by the humanized, HLA-disparate immune system and secondly, if these cells are efficient in bone regeneration. Cell-biomaterial interactions will be considered. Newborn NOD/SCID-IL-2γc-/- mice were therefore transplanted with human hematopoietic stem cells to reconstitute a human immune system.

Before investigating bone healing the phenotype of the bone NOD/SCID-IL2γc-/- mice has to be investigated. For comparison immunocompetent mice (BALB/CByJ) and several mice with different deficiencies of the immune system were used. In each mouse strain, mechanical properties of the bone (biomechanical analysis of the femora by the three-point-bending-test), bone density and structure (µCT-analysis) and cellular and metabolic characteristics (histomorphometric analysis of osteoblast/osteoclast number, bone formation rate etc.) were determined. These analyses are almost finished except the histological evaluations. Currently we are isolating cells (MSC, osteoblasts, osteoclasts) from each mouse strain to answer the question if the cells derived from immune deficient mice have an autonomous defect in cell proliferation and activity in comparison to the corresponding control cells.

The first results show no significant differences in the flexural rigidity of the femur of the NOD/SCID-IL2γc-/- mice in comparison to other mouse strains and µCT analysis revealed a lower bone mass in comparison to the corresponding BalbC control. Bone mineral density was higher in NOD/SCID-IL2γc-/- mice than in BalbC suggesting a decreased resorption activity of osteoclasts.

Immune reconstitution in NOD/SCID-IL2γc-/- mice using human hematopoietic stem cells was performed in Tübingen.

To improve engraftment rates, mice were irradiated prior to transplantation and received human Interleukin-7 to promote lymphocyte development. Human cells appear soon after stem cell transplantation. However, the percentage declines during the first 2 to 3 month after transplantation. This reduction is a common effect that is usually followed by a recovery of human leukocyte counts. The dominant lymphocyte subpopulations during the first 2 to3 month are B cells while T cells appear 3 to 4 month after stem cell transplantation and present the main subpopulation in later phases of human engraftment. For bone healing experiments, the first humanized mice were transferred to Ulm. Mice underwent surgery 9 to10 weeks after stem cell transplantation and were sacrificed 28 days later (week 13-14). Further experiments, using later time points post transplantation are currently performed. We have operated 26 mice successfully without prior stem cell transplantation. Currently, the bone healing is investigated after hematopoietic stem cell transplantation.

The experiments are still ongoing and should answer the question if bone defect healing is altered in NOD/SCID-IL2γc-/- mice and humanized NOD/SCID-IL2γc-/- mice in comparison to wild type mice. The preliminary experiments revealed no differences in the healing outcome after 28 days in the BalbC control and the non-transplanted NOD/SCID-IL2γc-/- mice. However, bone healing was delayed in humanized animals NOD/SCID-IL2γc-/- mice probably due to the irradiation performed before transplantation of hematopoetic stem cells. This will be investigated in further experiments.

For the treatment of bone lesions, human MSC isolated from marrow used for hematopoietic reconstitution (autologous) and from HLA-mismatched donor will be loaded on solid biomaterial and then implanted in bone defects. Femurs will be explanted and new bone formation will be analyzed as stated in Task 4.1. Inflammation parameters (i.e. interleukins, adhesion proteins, lymphocytes infiltration) and angiogenesis will be as well considered. A group of mice will receive MSC labeled with contrast agent loaded nanoparticles in order to establish a tool for in vivo tracking MSC by tomographic imaging MRI. A method for in vivo tracking of MP by non-invasive imaging will be established in the mouse model. The MP will be labeled by individually designed nanoparticles carrying high payloads of contrast agents specific for MRI or spectral CT tomographic imaging. (UNITUE, ULM). This model shall focus on feasibility and toxicity of in- vivo tracking of MP. The aim is to develop the method for application in the clinical trials. Effect of nanoparticles on functionality of MP will be studied with the repertoire of assays in WP3.

Task 6. Mimicking challenging clinical trials of bone regeneration with animal models

Regarding the last task of WP4, pre-clinical models of bone diseases have been started in particular regarding osteonecrosis both in the mini-pig and in the mouse model. For the first, we are setting-up and it is in progress a model with cryo-induction while for the latter steroid dosage schedule is under investigation within specific mouse strain.

3.2.4.2 Significant results of WP4 during the period

The WP4 of REBORNE is providing the following significant results:

- We provide novel potency assays combining human mesenchymal stem cells (MSC) and biomaterials to be translated into GMP settings of REBORNE. The combined observation from two independent research groups (EFS#2 and UNIMORE#12) using different modifications of osteogenic differentiation protocols was that differences resulting from either FBS (fetal bovine serum) or PLP (platelet) supplementation on expansion and differentiation meda did not alter the facts that *ex vivo* hMSC osteogenic potential was clearly driven using either BMP-2 or BMP-4 growth factors. In both cases, development of an osteoblastic phenotype was significant, occurring in different concentrations of FBS or PLP differentiation medium supplemented with recombinant human osteogenic inducing agents rhBMP-2 or rhBMP-4 in the presence or absence of dexamethasone.

- By using spectrophotometric analyses of MSC mineralization potential, we first provided quantitative assessment of the bone differentiation of MSC.

- In addition, we show for the first time that PLP supplementation is capable to drive a better osteogenic commitment rather than medium based on FBS in both adipose and marrow derived MSC isolated and expanded in large scale within the GMP facilities of REBORNE.

- Based on *in vitro* findings, we here propose a shorter differentiation protocol using GMP derived bone marrow and adipose MSC.

- We can monitor osteogenic differentiation *in vitro* with a panel of 10 markers and in particular with the following biomarkers: Collagen type IA1, RUNX2, DCN and DLX-5.

- DCN (Decorin) can be consider a predictive marker of bone differentiation by MSC and will be validated by further test wither *in vitro* or *in vivo*.

- MBCP+ granules are a valid biomaterial for the MSC interaction since they are capable to attract marrow and adipose MSC and maintain their proliferative and differentiation potential *in vitro*

- MBCP+ granules are a valid biomaterial for the clinical studies and are associated with a bone mineralization when combined with GMP-produced MSC *in vivo*

- The dose of cells and a contact time of one hour to induce *de novo* bone was determined to be 20 million hMSC per cm^3 of MBCP + granules

- We were able to obtain the clearance of the local ethical committees for animal experimentations

- We were able to standardize culture conditions for MSC isolated from marrow and adipose rabbit tissues.

- A novel flow-cytometry panel was uncovered to identify rabbit MSC *in vitro*. This will be extremely useful for the several pre-clinical models of bone regeneration that are foreseen in REBORNE.

- We were able to standardize culture conditions for MSC isolated from marrow mini-pig tissues.

- We were able to standardize culture conditions for MSC isolated from marrow sheep tissues.

- Our results showed that MSC *in vitro*-derived by using media containing pro-angiogenic factors (EGM2) are able to generate pericytes, to form vascular-like structures that other MSCs do not, and to give rise to adipocytes and osteo-

chondroblastic cells. There are strong evidences from these studies of a high degree of plasticity of EGM2-derived cells and that pericytic phenotype shall be crucial for bone regeneration *in vivo* notably through the increase of vascularisation.

- Under the immunological point of view, we standardized experimental methods to assess MSC immunomodulatory properties of MSC *ex-vivo* expanded from bone marrow (BM), adipose tissue (AT) and cord blood (CB) for clinical use. The effect of interaction of different immune effector cells (T, B, NK cells) with MSC was assessed in terms of inhibition of proliferation and cytotoxicity in response to non-specific stimuli.

- We successfully transplanted NOD/SCID-IL2$\gamma c^{-/-}$ mice with human hematpoietic stem cells. Additionally, we demonstrated that the operation procedure is feasible also in immune deficient mice and that bone healing can successfully occur in these mice.

All these significant results of WP4 were also included in the completed deliverables which have been up-loaded on the website:

- D4.1 Provide improved potency assays of bone regeneration for GMP-manufactured MSC and biomaterials

- D4.2 Provide standardized diagnostic *in vivo* and post-mortem read-out of bone re-growth

- D4.3 Provide pre-clinical reports based on CE labelled biomaterial and GMP-grade MSC

- D4.4 Report standardized animal MSC isolation and culture protocols

- D4.7 Identify cell combinations and *in vitro* conditions to support angio-osteogenesis

- D4.10 Identify proper cultures conditions enhancing immunomodulatory properties of MSC

3.2.4.3 Main deviations from Annex I

All the critical objectives of WP4 have been reached.

Other set of experiments related to tasks 1 and 4 within this WP will be performed to optimize the assay of bone differentiation testing other types of biomaterials provided by WP1.

There was a slight delay in finalizing the early deliverables of the project due to administrative issues related to the transferring of the grant at the different Institutions involved in REBORNE. These aspects are not having a major impact in the project prosecution and in the obtained data related to the first period of REBORNE activity.

Minor deviations were introduced and consist in delays in finalizing the experimental phases for few topics. All these are not related to the early clinical trials of REBORNE and these deviations from the original timetable will be corrected early in this current second year of activity. This is the list of the issues which will be finalized in this current year:

- FACS analyses are on-going to assess the integrins expression as parameter to be tested for a MSC-mediated bone repair mediated by biomaterials

- Introduction of more sensitive molecular analyses of MSC differentiation based on array techniques testing a wider court of genes related with osteogenic differentiation. Also, the expression on microRNA will also be concluded at the different stages of osteoblastic differentiation, providing a more precise signature of differentiation.

- Gene therapy approaches of bone regeneration by introducing into MSC genes or miRNA identified as capable to be associated with a greater osteogenesis

- Complex histological tests will be implemented for explants which have been already analyzed by µCT. Explants will be analyzed by histology in paraffin, methylmethacrylat resin testing, at the protein level, the markers (genes) which resulted predictive of bone formation and angiogenesis in vitro (Coll I, ALP, DCN, DLX5, BSP, OCN, BMP2, CD31, von willebrand factor).

- While in the annex 1 of REBORNE we wanted originally standardize the isolation of both adipose and marrow MSC for all the three involved animal species (rabbit, mini-pig and sheep). In the project execution, we restricted the working scenario so that adipose and marrow MSC were isolated only from rabbit while for the others species only the marrow source was considered. We presume this could be enough to start with the early pre-clinical studies. If necessary in the later REBORNE phase, we will also consider the adipose source. Ethical aspects on animal experimentation also drove this deviation.

3.2.4.4 Use of resources of WP4

Participant number	Participant short name	Staff effort (men-month)		Cost	
		Planned	Actual	Planned	Actual
1	**INSERM**	34,08	18,47	224 311 €	197 828 €
2	**EFS**	22,00	33,30	259 071 €	359 006 €
4	**CEA**	9,60	0,84	74 998 €	11 676 €
5	**POLICLINICO**	6,00	2,67	30 294 €	6 849 €
12	**UNIMORE**	27,50	12,99	227 800 €	191 963 €
15	**UNITUE**	9,00	9,75	92 899 €	138 536 €
16	**UULM**	17,25	15,39	123 360 €	117 602 €
TOTAL		**125,43**	**93,40**	**1 032 734 €**	**1 023 461 €**

The main deviations between actual and planned person months are related to a wrong effort planning at the beginning of the project. Tasks of Partner #4 CEA started lately and UNIMORE received the money very late due to some administrative mistakes.

3.2.5 WP5 – Orthopaedic clinical trials

3.2.5.1 Summary of progress towards objectives and details for each task of WP5 during the period

Work of WP5 during this first year included the following main objective:
Preparation of the first clinical trial (**Ortho1**), to be launched in the 2nd year.

This main objective included the following tasks:
Coordination of the clinical partners to prepare the trial after assigning the tasks as follows:

- OrthoCT1 STUDY DESIGN:
  - Draft Synopsis (partners #11, 13, 14)
  - Clinical Trial Protocol (CTP): input and subsequent review (partners #1, 3, 7, 11, 13, 14, 21, 23). Basic input from WP5.
  - Developing annexes of the CTP (WP5 with help of WP7).
  - Investigator brochure: input and subsequent review (partners #3, 5, 7, 14, 11, 16). Input from WP5 on data provided by WP1, 2, 3, and 4.
  - Informed consent - English core version to develop translations and national adaptations can be done by the sites (#13, 5, 7, 11, 16, 21).

- Other tasks assigned in the OrthoCT1 study: Among partners, the task list has been distributed in the managing of the study, particularly regarding Site qualification visits, Submission to Competent Authorities (CA) and Ethics Committees (EC), Investigator meeting, Medical monitoring, QA Audit, Audit of sites, Clinical study report , Statistical analysis.

- EudraCT number obtained: 2010-024257-37

- CRO negotiations: 3 Clinical Research Organizations have been asked for a budget in order to compete for the subcontract. The tender procedure, according to the European law, has been prepared.
- PROTOCOL: The developed protocol is annexed to this report (see attachment 1). Specific items requiring specific discussions among the partners, the supporting WPs and the coordinator include:
  - Number of patients and participating centres, according to the plan, and planned distribution of patients per centre.
  - Check of the availability, transportation and coordination between clinical centres and GMP facilities.
  - Define economical and statistical analysis
  - Refine ethical aspects in the protocol.

  - Define an independent monitoring committee
  - Define number of cells to be implanted.
  - Define the required degree of confidentiality and the appropriateness of identification in autologous cells to avoid mismatching.
  - Cooperate with coordinator (INSERM #1) for sponsorship of the study and insurance obtention.

- PRELIMINARY confirmation of adequacy regarding Coordination with GMP facilities.
  - Results on applying the preliminary bone marrow obtention procedure.
  - Support and discussion on the cell transportation between clinical centres and GMP facilities and back.
  - Discuss with WP2 the obtained cell expansion and refine the procedure.

As a conclusion, based on WP5 work during this first year, 5 clinical centres (UAM #11, H.M. #7, CHU TOURS #14, UULM #16, IOR #21) are ready to submit the applications to Ethical Committees when the Investigator Brochure about the investigational product is completed, in coordination with WP1, 2, 3 and 4. The planning includes recruitment of 6 patients per centre.

3.2.5.2 Significant results of WP5 during the period

This period in WP5 was related to the preparation of the clinical trial protocol and one significant result is the CTP for ORTHO1, included as an Annex to this report.

3.2.5.3 Main deviations from Annex I

The main deviation expected for the following year regards the potential recruitment of partner UMFTVB #13, which may not be ready for this ORTHO1 study. However, this has been managed by redistributing the 5 patients planned in UMFTVB #13 to other clinical centres. The other partners will recruit 6 instead of the planned 5 patients per centre. This deviation can be easily compensated. The mentioned partner #13 has nevertheless developed intensive work in this first year regarding the study preparation.

3.2.5.4 Use of resources of WP5

Participant number	Participant short name	Staff effort (men-month)		Cost	
		Planned	Actual	Planned	Actual
7	AP HP	2,40	1,33	19 920 €	39 144 €
11	UAM	4,20	8,27	58 292 €	99 474 €
13	UMFTVB	2,70	0,00	20 880 €	1 463 €
14	CHU TOURS	2,40	0,28	14 940 €	1 972 €
15	UNITUE	1,80	0,00	18 580 €	0 €
16	UULM	3,00	0,00	0 €	1 041 €
21	IOR	4,20	3,37	48 424 €	19 325 €
23	AOU MEYER	1,20	4,57	11 840 €	14 208 €
TOTAL		21,90	17,81	192 876 €	176 626 €

The main deviations between actual and planned person months is mainly due to the facts that UAM as the WP leader worked hard on the Clinical trial Protocol and that the other participants' tasks are focused on the clinical trials that have not started yet.

3.2.6 WP6 – Maxillo-facial clinical trials

3.2.6.1 Summary of progress towards objectives and details for each task of WP6 during the period

The aim of WP6 is to validate the efficacy of the biomaterial-cell combination designed by WPs 2, 3 and 4, through 2 maxillofacial clinical trials.

Task 1: Bone augmentation before dental implants
The developed protocol is annexed to this report (see attachment 2).

Task 2: Bone reconstruction of clef palates in adults or children
Not yet applicable

3.2.6.2 Significant results of WP6 during the period

1. ***To determinate the most clinically relevant indication***

(CHU NANTES #6, ULG – PARO #24, UNIVR #17, UiB #19).
The study will concern non aesthetic areas in inferior and superior jaws with a post remaining tooth. It will consist in a vertical and transversal bone augmentation of the mandible bone using calcium phosphate granules, collagen membrane and autologous MSCs prior to dental implants.

2. To determine the principal and secondary objectives of the study
(CHU NANTES #6, ULG – PARO #24, UNIVR #17, UiB #19).

The principal objective is to assess whether or not it is possible to insert an implant in the reconstructed area 6 months after the graft. The decision will be made based on radiological and clinical examinations.

3. To determine the most suitable (ease of handling) combination of biomaterials and cells for the targeted clinical application
(CHU NANTES #6, BIOMATLANTE #3)

- Granules size of MBCP+ will be 1-2 mm.
- Cells will be suspended with a concentration of 20 millions per ml in human albumin (Vialebex™ 4%).
- Ratio of biomaterials and cells for the grafting procedure: 1 cm3 or 0.5 g of non hydrated MBCP+ granules 1-2 mm and 20 million autologous hMSCs in 1 ml Albumin.
- Medical device: plastic syringe with operculum provided by BIOMATLANTE containing 5 ml biomaterial MBCP+ 1-2 mm (or less).

4. To validate the grafting procedure
(CHU NANTES #6, BIOMATLANTE #3)

This procedure was performed on a corpse using the MBCP+ granules (1-2 mm), and the absorbable membrane provided by BIOMATLANTE. The procedure was validated on the upper and lower jaw.

5. To choose the dental implant features
(CHU NANTES #6, ULG – PARO #24, UNIVR #17, UiB #19)

The implants selected by the clinicians for the study are bone level Regular CrossFit™ implants manufactured by Straumann® or implants with same features provided by another manufacturer. There is sufficient clinical perspective with Straumann® implants for them to be employed in the project and they are currently used by the most of centers participating in the study.

The bone level type implants were selected because of the reliability of the healing method in two stages that should allow better integration of the implant in the grafted biomaterials.

6. To validate the bone marrow harvesting protocol
(CHU NANTES #6, UAM #11, EFS #2)

This form was included in the clinical protocol annexes.

7. To evaluate the radiological exams for the bone formation assessment
(CHU NANTES #6)

A CT scan and a Cone Beam CT were performed on a corpse before and after a grafting procedure with the biomaterials, the membrane, and some non absorbable titanium pins. The radiological SOP was validated by the physicians and the data manager

8. To write and translate the clinical protocol
(CHU NANTES #6, ULG – PARO #24, UNIVR #17, UiB #19, BIOMATLANTE #3, EFS #2)

The clinical form has been written and translated for dissemination and approval by the other WPs. The patient Information sheet / Consent form and Case Report form have been written.

9. To validate the histological SOP
(CHU NANTES #6)

Tissues transportation, samples preparation, and assessment criterion were discussed with a pathologist physician.

10. To contact GMP and clinical research local facilities people in countries involved in the first clinical trial
(CHU NANTES #6)

Norway team has CRA and will be able to manage the Ethical Committee and regulatory Authority submission.

For Belgium and Italy, these data have to be affirmed.

11. Projected budget
(CHU NANTES #6)

The forecast budget for the first maxillofacial clinical trial was estimated. It should reach more than 350 k€ for CHU NANTES #6. This budget draft must be revised by the sponsor and should be modified depending on the need for a CRO.

The budget for the second maxillofacial clinical trial is not estimated yet.

12. WP6 first delivrable
(CHU NANTES #6, ULG – PARO #24, UNIVR #17, UiB #19).

The D6.1 Maxillo1: Developed protocol and Ethical Committee approval for each participating centre is drafted but is waiting for data from WP2 and WP4. The forecast delivery date is Month 18.

3.2.6.3 Main deviations from Annex I

Task 1. Vertical and sagital bone augmentation in the mandible using calcium phosphate granules, membrane and autologous MSCs prior to dental implants (CHU NANTES #6, ULG – PARO #24, UNIVR #17, UiB #19)

In the technical annex I, the following protocol was proposed:

Bone augmentation before dental implants:
We propose to use MBCP granules and collagen membrane for vertical and sagital (1) bone augmentation in the premaxillary (2) or mandible. At the time of surgery, bone marrow will be harvested under local anaesthesia from the maxillary. Adipose tissue could be also used depending on pre clinical results (3). After expansion and ostegenic differentiation (4), autologous cells will be injected through the gingiva (5) in the defects filled with biomaterial. The injection should be done about 3 weeks after the first surgery(5). At this stage, post surgical inflammation and vascularisation should be in place ensuring a good nutrient supply for the cells. In addition, the collagen membrane should prevent tissue fibrosis and favour osteogenesis. Four months later (6), a CT scan should confirm sufficient bone stock for dental implant. A small biopsy will be harvested and analyzed by histology prior to dental implant insertion. The implant stability will be measured by suing radio frequency analysis (RFA) at the time of implantation and 3 months later About 20 patients (7) /clinical centre will be included in this study giving a total of 60 patients (7) for Nantes, Verona, Bergen and Liège.

Deliverables (brief description and month of delivery) – From Annex I approved by Commission on 15th Oct 2009.
D6.1: Maxillo1: Developed protocol and Ethical Committee approval for each participating center –Month 13 (8)
D6.2: Maxillo 1: Completed recruitment and treatment delivery- Month 24 (8)
D6.3: Maxillo 1: Primary outcome measure: Proportion of patients with sufficient bone stock for dental implant placement 4 months after first surgery: clinical, radiographic CT scans and histology - Month 28 (9
D6.4: Maxillo 1: secondary outcome measure: Proportion of patients with sufficient dental implant stability after osseointegration 3 months after second surgery - Month 36 (10)

On the basis of discussions between surgeons as well as data available from WP2 and WP4, we have decided to make the following deviations from the original first clinical trial as it was described in the technical annex:

(1) "We propose to use MBCP granules and collagen membrane for vertical **and sagital** bone augmentation … "

→ *Reasons for deviations:* transversal, and not sagital bone augmentation was chosen by all the European clinician for this first maxillofacial clinical trial as the best indication.

→ *Impact on other tasks, available resources and planning: n*ot applicable

(2) "We propose to use MBCP granules and collagen membrane for vertical and sagital bone augmentation in the **premaxillary** or mandible"

→ *Reasons for deviations:* all the European clinician for this first maxillofacial clinical trial decided to avoid the aesthetics area

→ *Impact on other tasks, available resources and planning: n*ot applicable

(3) "**Adipose tissue could be also used depending on pre clinical results**"

→ *Reasons for deviations:* preclinical results not available

→ *Impact on other tasks, available resources and planning:* not applicable

(4) "… osteogenic differentiation"

→ *Reasons for deviations:* preclinical validation (GMP conditions) not available

→ *Impact on other tasks, available resources and planning:* not applicable

(5) "autologous cells will be injected through the gingiva"

→ *Reasons for deviations:* preclinical validation (GMP conditions) not available

→ *Impact on other tasks, available resources and planning:* not applicable

(6) "Four months later …"

→ *Reasons for deviations:* regards to the recent literature, a 9 months healing delay should be preferable.

→ *Impact on other tasks, available resources and planning:* further timing spots are postponed (5 months after the previous date)

(7) " … and 3 months later"

→ *Reasons for deviations:* regards to the recent literature, the most clinically relevant period for full implant integration is 3 months for the mandible and 6 months for the upper jaw.

→ *Impact on other tasks, available resources and planning:* not applicable,

(8) "About 20 patients …", " 60 patients"

→ *Reasons for deviations :* as the study is therefore a descriptive study to assess the value and innocuousness of hybrid bone substitutes in humans, it is impossible to justify the number of patients to be included. The planed number decided by all the European clinician for this first maxillofacial clinical trial depending the recruitment period, is 10 per centre (a total of 40 patients)

→ *Impact on other tasks, available resources and planning:* not applicable

(9) D6.1: Developed protocol and Ethical Committee approval for each participating center –Month 13

→ *Reasons for deviations:* experimental validation of the material and cells combination not yet available, waiting for WP2 and WP4 results.

→ *Impact on other tasks, available resources and planning:* Forecast delivery date for D6.1 should be Month 18 depending on experimental results. Further timing spots are postponed of 5 months.

(10) D6.3: Maxillo 1: Primary outcome measure: Proportion of patients with sufficient bone stock for dental implant placement 4 months after first surgery: clinical, radiographic CT scans and histology - Month 28

→ *Reasons for deviations:* please refer (6), (8) and (9).

→ *Impact on other tasks, available resources and planning:* please refer (6) , (8) and (9). Forecast delivery date for D6.3 is Month 38.

3.2.6.4 Use of resources of WP6

Participant number	Participant short name	Staff effort (men-month)		Cost	
		Planned	Actual	Planned	Actual
6	**CHU NANTES**	7,44	16,83	88 148 €	72 004 €
17	**UNIVR**	3,50	0,47	33 308 €	4 962 €
19	**UiB**	3,50	5,40	34 896 €	45 381 €
20	**UMC UTRECHT**	2,70	0,62	26 656 €	8 451 €
24	**ULG PARO**	3,50	0,24	34 896 €	4 876 €
TOTAL		**20,64**	**23,56**	**217 904 €**	**135 674 €**

The main deviations between actual and planned person months is mainly due to the facts that CHU NANTES as the WP leader worked hard on the Clinical trial Protocol, UiB worked hard on contacting the personnel and departments involved in the first clinical trial, recruiting patients and preparing the application for the ethical clearance from the local authority in Bergen and that the other participants' tasks focused on the clinical trials that have not started yet.

3.2.7 WP7 – Ethics, regulatory, legal issues and dissemination

3.2.7.1 Summary of progress towards objectives and details for each task of WP7 during the period

For the whole duration of REBORNE project, the main objectives of WP 7 are to establish the general ethical perspectives and legal framework in preclinical and clinical R&D of new biomedical engineered products based on allogenic and autologous adult human MSC and biomaterials, as well as to disseminate and exploit the foreground generated within the project.

In establishing the ethical perspectives for advanced therapies regarding the experiments carried out on both humans and animals, the fundamental ethical principles, as well as the protection of human rights and of welfare of animals were taken into account. The role of ethical committees in the process of evaluation and approval of animal experimentation and clinical trials on human subjects has been reviewed.

Regarding the legal framework, a complete overview of the legal instruments in the field of medicinal products for human use, covering also the laws regulating the research on human subjects and on animals was performed. Several models of informed consent and patient information forms for clinical trials within REBORNE were proposed.

Dissemination activities consist not only in the participation of different members of REBORNE in scientific meetings reporting their results and publication of their work in

journals, but also in the significant involvement of REBORNE members in the organization of the *1st European Conference on Mesenchymal Stem Cells* held in Toulouse, in November 18-20, 2010. (http://www.mes-stem-cells.com/). A website dedicated to REBORNE project was launched in May 2010 (http://www.reborne.org/)

3.2.7.2 Significant results of WP7 during the period

For the reporting period, work within WP 7 resulted in the deliverables prepared by partner 13, University of Medicine and Pharmacy Victor Babes Timisoara, the WP7 coordinator, and partner 18, ALCIMED, with the support of the partners involved in this work-package. The deliverables due to this period were:

- D7.1 REBORNE WP7 Action Plan
- D7.2 Listing Of Local / Regional / National Ethics Committees in the Countries of Teams Involved in REBORNE
- D7.3 Listing of Local / Regional / National Regulatory Authorities in the Countries of Teams Involved in REBORNE
- D7.4 REBORNE Exploitation Guidelines
- D7.5 Report on Legal Framework on Preclinical Trials Involving Animal Use
- D7.6 Report on Approval Procedure and Core Submission Package for Regulatory Authorities for Preclinical Trials
- D7.7 REBORNE Plan for Using and Disseminating Knowledge
- D7.8 Report on Review and Voting Procedure and Core Submission Package for Ethical Committees for Preclinical Trials
- D7.9 Report on Current Status of Ethical Issues in the EU and World-wide, as well as in the Countries of Teams Involved in the Project
- D7.10 Website Dedicated to the REBORNE Project
- D7.11 Report on Legal Framework on Harvesting, Banking and Use of Human MSC
- D7.12 Report on Ethical Issues for Harvesting, Banking and Use of Human MSC
- D7.13 Report on Approval Procedure and Core Submission Package for Regulatory Authorities for Clinical Trials
- D7.14 Report on Review and Voting Procedure and Core Submission Package for Ethical Committees for Clinical Trials
- D7.15 Report on Legal Framework on Clinical Trials Involving Human Subjects Treated with MSC and Biomaterials
- D7.16 First Annual Report of the Ethical Advisory Board

D7.1
This report, done by UMFVBT, details the action plan for the work package 7 of the REBORNE project. It gives the objectives to be reached and tasks to be performed within WP7, as well as the interactions with partners in other work packages.

D7.2
It lists the Ethics Committees to which partners of REBORNE project submit their protocols for ethical review in order to get approval for the clinical and preclinical trials they conduct. The table has been produced by UMFVBT with the support of the other partners in WP 7.

D7.3
The report lists the Regulatory Authorities to which partners of REBORNE project submit their protocols for ethical review in order to get approval for the clinical and preclinical trials they conduct. The table has been produced by UMFVBT with the support of the other partners in WP 7.

D7.4
This document presents two main sections: a preliminary list of the products to be developed within REBORNE that may have commercial or industrial applications, and a preliminary market overview of the products to be tested within REBORNE clinical trials. The deliverable was due to month 3 (March 2010), but it has not been delivered due to a long validation process: the deliverable was drafted by ALCIMED in May 2010, and it entered into an internal validation process that resulted in a slightly modified version that is at present being validated internally. The final version is expected to be delivered in month 15 (March 2011). This delay does not affect any other task in the project.

D7.5
This report focuses on the legal framework on preclinical trials involving animal use within EU. The aim was to provide the consortium with detailed information on the laws and guidelines on preclinical trials. The report discusses several ethical issues which are still on debate and provides data regarding the laws, recommendations and guidelines needed to conduct ethical research using animals. Different Member States regulations are also mentioned. The first version was generated by UMFVBT. Since then, two revisions were made, first one in month 4 in order to add the corrections suggested by INSERM, and the second one in month 12, by adding information provided by UNIMORE.

D7.6
The report gives information on the approval procedure and core submission package for regulatory authorities for preclinical trials in the countries of the partners involved in preclinical trials. The aim was to provide the consortium with detailed information on the procedure and documents needed prior to start of any preclinical trial. This helps the scientists to prepare well documented and written packages for regulatory authorities in order to avoid the unnecessary time loss for such an activity if they would have to gather this information by themselves. The document was prepared by UMFVBT and then revised following the suggestions from the partners.

D.7.7
The document, done by ALCIMED, summarises the consortium's strategy and concrete actions to disseminate the foreground generated by REBORNE. It presents the roles of project partners in dissemination and the different categories of targets for communication. The methods of communication and the tools developed (logo and templates for documents) were also described.

D7.8
This report focuses on review and voting procedure and core submission package for Ethical committees for preclinical trials. The aim was to provide the consortium with information on the review and voting procedure and documents needed prior to start of any preclinical trial. Done by UMFVBT based on data provided by partners involved in preclinical trials, it has been revised for the last time in month 12.

D7.9
The report on the current status of ethical issues in the European Union and worldwide is a review of the ethics dealing with medical research. It focuses on research involving human subjects and experiments on animals in some countries, as well as in some regions. The basic ethical principles and the way they are followed around the world are highlighted, while the ethical requirements on clinical and preclinical trials are detailed. The document was done by UMFVBT and reviewed by partners.

D7.10
The website dedicated to REBORNE project (http://www.reborne.org/) was launched in June 2010 and comprises a public section and a private one. In the open-access section there are general information, such as a short description of the project and the presentation of consortium, with links to the official web pages of the partners. The private section is designed to allow partners sharing their work.

D7.11
This report, done by UMFVBT, reviews the laws and regulations related to medicinal products within the European Union. It starts with the first pharmaceutical directive in the field, and tracks the historical development of the legal framework that led to the establishment of the Community Code relating to the medicinal products for human use. It also gives information on the creation of the European Medicines Agency, which acts as a key player in the field. At the end of the document, the three directives focusing on advanced therapy medicinal products, standards and technical requirements for each step in the human tissue and cell application process are described, as well as the regulation establishing the creation of the Committee for Advanced Therapies within the European Medicines Agency.

D7.12
The document addresses the ethical issues related to the harvesting, banking and use of human MSC. The embryonic stem cells, as well as adult stem cells use and the ethical questions raised by research involving them were described. The ethical conduct regarding informed consent, privacy/data protection, risk/benefit assessment, protection of subject's health and transparency regarding results have been also approached by UMFVBT. The report has three annexes containing proposed models of Informed Consent forms for: donation (adipose tissue, amniotic membrane, bone marrow, cord blood); orthopaedic clinical trials (ORTHO 1, ORTHO 2, ORTHO 3 and Patient Information sheets, respectively); maxillo-facial clinical trials (MAXILLO 1, MAXILLO 2 + Patient Information sheets, respectively).

D7.13
This report focuses on the approval procedure and core submission package for regulatory authorities for clinical trials in the countries of partners involved in clinical trials. The aim was to provide the consortium with detailed information on the procedure and documents needed prior to start of any clinical trial. This will help the scientists to prepare well documented and written packages for regulatory authorities in order to avoid the unnecessary time loss for such an activity if they would have to gather this information by themselves. It will also act as a database to which the partners can refer to each and every time they need to get approval from authorities for carrying out their trials. It was done by UMFVBT with the support of partners.

D7.14
The aim of this report was to provide the consortium with detailed information on the review and voting procedure, as well as on documents to be submitted to Ethical Committees prior to start of any clinical trial. Partners have provided data to the UMFVBT team, who was responsible for writing the document. The report has been revised once.

D7.15
The review of the main legal instruments related to the conduct of clinical trials in the European Union was performed by UMFVBT. It provides information on the legislation applicable to clinical trials in general and particularly to clinical trials for advanced therapy medicinal products, under which the combination of MSC and biomaterials falls.

D7.16
Given that the Ethical Advisory Board meets for the first time at the First Governing Board Meeting of REBORNE project to take place in Nantes, on 31st January and 1st February 2011, this report has to be delayed. So far, the members of EAB were provided with the reports done in WP 7 relating to ethical issues.

3.2.7.3 Main deviations from Annex I

D7.16 First Annual Report of the Ethical Advisory Board has to be delayed as the Ethical Advisory Board of REBORNE meets for the first time at the First Governing Board Meeting to take place in Nantes, on 31st January and 1st February 2011. This delay will have no impact on other tasks, available resources and planning. D7.4 Exploitation Guidelines is delayed, due to a long internal validation process, at it is explained before. This delay will have no impact on other tasks, available resources and planning.

3.2.7.4 Use of resources of WP7

Participant number	Participant short name	Staff effort (men-month)		Cost	
		Planned	Actual	Planned	Actual
5	**POLICLINICO**	0,20	2,00	1 200 €	7 920 €
6	**CHU NANTES**	0,70	0,57	15 000 €	2 192 €
10	**UPC**	0,32	1,28	2 265 €	4 524 €
12	**UNIMORE**	0,60	0,60	2 368 €	7 329 €
13	**UMFTVB**	4,80	6,64	20 200 €	36 383 €
18	**ALCIMED**	0,70	2,51	12 804 €	25 811 €
TOTAL		**7,32**	**13,60**	**53 837 €**	**84 159 €**

The main deviations between actual and planned person months are related to a wrong effort planning at the beginning of the project; indeed, most of the WP7 deliverables are to be delivered in the first year.

3.3 Project Management during the Period

The Grant Agreement was received from the European Commission in October 2009; it was signed by the legal representative of the coordinator and sent back to the European Commission.The Grant Agreement was signed by the European Commission in November 2009, and all the beneficiaries signed the Form A within the following 45 days.

3.3.1.1 Consortium agreement

The Consortium Agreement was produced during the first weeks of the project based on the DESCA model. Nevertheless, several modifications were requested by different beneficiaries, which led to the writing of a modified version of the Consortium Agreement, in order to integrate all the suggestions proposed by the beneficiaries. This action has originated several interactions between the management team and the different beneficiaries and a final version was written by INSERM Transfert. This version of the Consortium Agreement is at present being signed by the whole consortium.

3.3.1.2 Distribution of the EC contribution to the beneficiaries

The prefinancing for the project was received on November 29th 2009 by the coordinator, who made a first transfer of funds to the different beneficiaries in February 2010.

3.3.1.3 Internal reporting

In order to gather information about the financial status of the project in a regular basis, the management team has set up an internal reporting procedure:

- Internal financial reporting: An internal financial report is demanded to all the beneficiaries every 6 months. This internal report, which includes more detailed information than the Form C, allows the management team to have a close follow-up of the financial issues of the project. Internal financial reports have been collected for the periods Jan10-Jun10 and Jan10-Dec10.

3.3.1.4 Project Meetings

The management team is in charge of organizing and coordinating the different project meetings: deciding the dates and the venues of the different meetings (in cooperation with the WP leaders and the rest of beneficiaries), informing the attendants in due time, producing and sending the agenda, producing and sending the meeting report after the meeting is hold and dealing with main logistic issues.
Different kinds of meetings have been organized during the first 12 months of the project, involving different beneficiaries and with different purposes.

- Government Board Meetings

Governing Board meetings are hold with an annual basis, with the participation of all the beneficiaries. These meetings are the place for all the beneficiaries to share the results obtained with the rest of the consortium and to decide on the orientation of the project.
During the first 12 month of the project, a Governing Board Meeting has been hold: the kick-off meeting, held the 14-15th of January 2010.

- Executive Committee meetings

Executive Committee meetings are attended by the management team and the WP leaders. The main objectives of these meetings are to assure a good technical and scientific coordination of the project, as well as to analyse and approve results and follow-up the project advances.
During the first 12 months of the project, two Executive Committee Meetings have been organized on the 16th of April 2010 and on the 28th of September 2010.

- Management Team meetings

Management Team Meetings are hold in a regular basis with the participation of the coordinator (INSERM #1), the co-coordinator (EFS #2) and the Project's Office (ALCIMED #18), with the aim of following the day-to-day management of the project.
During the first 12 months of the project, 4 Management Team Meetings have been held, most of them as telephone conferences. In addition, multiple informal meetings have been between the members of the management teams, most of them telephonic.

- Other meetings

Several informal contacts between the WP leaders took place, particularly a conference call in September 2010 for ensuring the good and effective cooperation of each other concerning the WP4.

A meeting focused on clinical aspects took place in Toulouse on the sidelines of the conference on mesenchymal stem cells; the objective was to gather clinicians to discuss the protocols.

- List of project meetings, dates and venues

LIST OF PROJECT MEETINGS, DATES AND VENUES DURING THE FIRST REPORTING PERIOD

Type of meeting	Date	Venue	Attendants
Kick-off meeting	14th-15th January 2010	Paris, France	All beneficiaries
Executive Committee meeting 1	16th April 2010	Paris, France	Coordinator, co-coordinator, Project Office and WP leaders
Executive Committee meeting 2	28th September 2010	Paris, France	Coordinator, co-coordinator, Project Office and WP leaders
Management Meeting 1	26th January 2010	Phone conference	Coordinator, co-coordinator and Project Office
Management Meeting 2	9th March 2010	Phone conference	Coordinator, co-coordinator and Project Office
Management Meeting 3	30th March 2010	Phone conference	Coordinator, co-coordinator and Project Office

Management Meeting 4	6th May 2010	Phone Conference	Coordinator, co-coordinator and Project Office
Management Meeting 5	25th June 2010	Phone conference	Coordinator, co-coordinator and Project Office
Management Meeting 6	7th September 2010	Phone conference	Coordinator, co-coordinator and Project Office
Management Meeting 7	13th September 2010	Phone conference	Coordinator, co-coordinator and Project Office
Meeting on clinical trials	20th November 2010	Toulouse	Coordinator, co-coordinator and WP leaders
1st Annual Meeting	*31th-1th January-February 2011*	*Nantes, France*	*All beneficiaries*

3.3.1.5 Follow-up of project deliverables and milestones

One of the tasks of the management team is to follow-up the advancement of the project and its status. One of the main tools used for this purpose are the deliverables and milestones tables, which are reviewed at each Executive Committee Meeting, as well as more usually during the management Team Meetings. For more details on this task, refer to section 4.

3.3.1.6 Development of the project website

REBORNE project portal has two main parts: a private portal, which has an access controlled by a user name and a password in order to restrict its access to project beneficiaries, and a public website, accessible by anyone having an Internet access.
Both the public and private parts of the website were set up in June 2010 and its URL is: www.reborne.org.

The main purpose of the private site is to provide a place for an efficient and seamless document sharing among the different beneficiaries. Besides, the site provides other functionalities which aim at improving the communication within the consortium.

The main functionalities of the private site are the following:

- Calendar: the site provides a calendar where important dates are announced.
- Address Book: the site contains a complete an updated list with all the participants of the project and their contact details.
- File Manager: this functionality allows the beneficiaries to share documents related to the project. The documents are organized in different folders; currently, the site contains one folder for each of the Work-Packages, as well as different folders for the meeting documents, and the documents related to administrative and financial issues.

The public website contains general information about the project and Bone regeneration and new biomedical engineering approaches. The content of the public website is continuously being updated and improved in order to offer to the public visiting it an up-to-date vision of the project status and advances.

Currently, the public website has seven main sections:

- Home: a welcome page summing up what REBORNE is
- Introduction: a general description of the project and of Bone regeneration and new biomedical engineering approaches
- Presentation: an overview of the geographic distribution of the beneficiaries of the projects and a brief presentation of each of them. The dynamic map of Europe with participants allows to click on logos and link to the corresponding websites
- News: a list of various events concerning REBORNE including the press release of the start of the project. This press release has been distributed through European media. While participants present their results at international conferences, the information is indicated in the news
- Links: a list of interesting links related to the project and bone defects: scientific societies, ethical and regulatory bodies and other European projects relative to the field of regenerative medicine
- Recruitment: jobs offered by participants are posted for a direct application of potential candidates

- Contact: the name, address, telephone and emails of coordinators are indicated there

3.3.1.7 Constitution of the Scientific Advisory Board and the Ethical Advisory Board

The Management Team, in close collaboration with WP7 (Ethical, regulatory, legal and dissemination issues) has set up the Scientific and the Ethical Advisory Boards for the project. These boards are currently composed of the following people:

Ethical Advisory Board:

- Prof. Alberto García JD (UNESCO Chair in Bioethics and Human Rights, University of Vatican, Rome, Italy)
- Prof. Isabel Varela-Nieto (Senior Scientist, Instituto de Investigaciones Biomédicas Alberto Sols, CSIS-UAM)
- Dr. Hélène Grandjean (INSERM U558 Director, Faculté de Médecine de Toulouse)

Scientific Advisory Board:

- Prof. Dr. Clemens van Blitterswijk (Department of Tissue Regeneration, University of Twente, Faculty Science & Technology Institute for Biomedical Technology Drienerlolaan)
- Prof. Dr. Frank Luyten (Chairman Division of Rheumatology Department of Musculoskeletal Sciences)

3.3.1.8 Management issues related to clinical trials

In order to prepare the clinical trials, the following management issues have been performed during the reporting period:

- EuraCT numbers have been obtained for the clinical trials ORTHO1 (2010-024257-37) and ORTHO2 (2010-024258-13).
- 3 Clinical Research Organizations have been asked for a budget in order to compete for the subcontract. The tender procedure, according to the European law, has been prepared and will be launched in the coming weeks.

3.3.1.9 Communication between beneficiaries

In the context of the project, the beneficiaries can make use of many different means and channels to communicate among them. This communication is made in different levels and with different objectives.

The management team (coordinator, co-coordinator and Project Office) are continuously in contact, mainly by phone or by email. This continuous contact assures an effective global management of the project and allows detecting any possible problem or deviation from the Work Program. Most of the administrative and financial issues related to the project are discussed at this level.

The Management team has a fluid communication with the WP leaders, mainly by email and during the Executive Committee Meetings. This communication is essential to assure a good scientific management of the project.

The WP leaders are in contact with the members of their respective WPs, mainly by phone and email, to share information about the advances of the work.

General issues about the project, as well as all the questions involving the whole consortium, are communicated to all the beneficiaries via the management team, mainly by email or during the Governing Board Meetings.

Besides these communication channels, all the beneficiaries keep frequent informal contacts with the beneficiaries with whom they work closely, mainly by phone and email.

In order to assure a good communication among the consortium, the project provides the beneficiaries with different tools that support and complement more standard means such as the phone and the email.

The main tool to support this communication is the internal website, where beneficiaries can easily share documents related to the project. The internal website provides other useful tools, such as an updated list of contacts with the name and the contact details of all the participants in the project.

3.3.1.10 Management problems occurred during the reporting period and solutions applied

One of the main management problems occurring during the first 12 months of the project has been related to the Consortium Agreement, since many requests had been addressed to modify it which has taken a long time.

3.3.1.11 Changes in the consortium

Changes to the legal status of the beneficiaries
Three beneficiaries have changed their legal status during the first 12 months of the project:

- University Verona (partner #17): this beneficiary has undergone several changes during the period; see attachment 3 for official documents.
    - a change in the name of the Department: from “Department of Clinical and Experimental Medicine” to “Department of Medicine”
    - a change of the authorised representative: the new authorized representative is Prof Antonio Lupo.

- POLICLINICO (partner #5): the beneficiary has changed its legal name and its authorized representative (Lugi Macchi); see attachment 4 for official documents.

- UAM (partner #11) has clarified the situation of its third party SERMAS:
  - "Universidad Autónoma de Madrid" (UAM), as a partner in the Project REBORNE (partner #11), takes part in this project along with the "Hospital Puerta de Hierro", whose legal entity is SERMAS (Servicio Madrileño de Salud). SERMAS participates as a Third Party (included in clause 10 of the Grant Agreement). SERMAS, a legal entity that covers all public university hospitals in Madrid has delegated the research performed by "Hospital Puerta de Hierro" and its management to FUNDACIÓN HOSPITAL "PUERTA DE HIERRO" by means of one Agreement included in attachment 5.

3.4 Explanation of the Use of Resources

Personnel, subcontracting and other major Direct cost items for Beneficiary 1 (INSERM) Year 1			
Work Package	**Item description**	**Amount (€)**	**Explanations**
WP0	Personnel cost	43793.40	Management and administration of the project: • 1 Scientist in charge (Pierre LAYROLLE) • 1 administrative assistant (Annie BECKER; working 2/5 days a week during the first semester and then 3/5 days a week)
WP1	Personnel cost	15800.44	WP1 tasks : • 1 researcher (Guy DACULSI)
WP4	Personnel cost	69099.81	WP4 tasks: • 1 Scientist in charge (Pierre LAYROLLE) • 1 Engineer Assistant in histology (Jérôme AMIAUD) • 1 Engineer Assistant in cells culture (Audrey RENAUD)
WP0	Other eligible cost	10806.00	• 1 Computer needed for management during travels • Creation and development of the REBORNE website • Press release
WP1	Other eligible cost	1871.27	Consumables for the laboratory
WP4	Other eligible cost	54542.69	• laboratory consomables • small equipment
WP0	Travel cost	14328.83	• Kick-off Meeting of the project - January 2010 PARIS (organization for all the beneficiary) • Congress MSC TOULOUSE 17/11/2010 (Pierre LAYROLLE) • Congress Promotion des Etudes Cliniques PARIS 16/03/2010 (Pierre LAYROLLE) • Meeting Reborne PARIS 28-29/09/2010 (Pierre LAYROLLE)
TOTAL DIRECT COST		**210242.44**	
Indirect cost		126145	*60% rate*
TOTAL COST		**336387.44**	

Personnel, subcontracting and other major Direct cost items for Third Party Beneficiary 1 (Université de Nantes) for the period			
Work Package	**Item description**	**Amount (€)**	**Explanations**
WP0	Personnel cost	0	
WP0	Other eligible cost	0	
WP0	Travel cost	0	
TOTAL DIRECT COST		**0**	
Indirect cost		0	*60% flat rate*
TOTAL COST		**0**	

Personnel, subcontracting and other major Direct cost items for Beneficiary 2 (EFS) for the period			
Work Package	**Item description**	**Amount (€)**	**Explanations**
WP2	Personnel cost	22129.84	WP2 tasks: • 1 Assistant (Gwellaouen BODIVIT) • 3 Technicians (Christine CARENA, Marilyn GOMEZ, Aurélie BLONDY) • 1 research engineer (Mélanie GADELORGE, • 1 laboratory head (Philippe BOURIN) • 2 researchers (Nathalie CHEVALLIER, Sandrine FLEURY)
WP3	Personnel cost	21213.40	WP2 tasks : • 1 research engineer (Joelle DULONG; full time then 1/5 part time from September 2011) • 1 technician (Isabelle BEZIER; from August to December 2010)
WP4	Personnel cost	146269.09	WP4 tasks: • 2 assistants (Gwellaouen BODIVIT, Laura COQUELIN) • 2 PhD (Alexandre POIGNARD, Julie LEOTOT) • 2 researchers (Frédéric DESCHASEAUX, Nathalie CHEVALLIER) • 2 laboratory heads (Luc SENSEBE, Hélène ROUARD) • 1 engineer (Audrey VARIN) • 2 research technicians (Alain LANGONNE, Angélique RICO)
WP2	Other eligible cost	46397.64	• Products and materials for tissue culture and histology • laboratory consumables
WP3	Other eligible cost	9530.38	laboratory consumables
WP4	Other eligible cost	113413.55	• Products and materials, laboratory consumables • Rack -80°C : DOMETIC n° 450077009299522 (storage) • cryode : ERBE n°4500763689 10FAC06316 (to induce a mini pig model)
WP4	Material cost	15272.14	• Mini-pig : Cegav n°4500750304

WP2	Travel cost	2159.30	• TaqMan PCR array : Life technologies applied biosystems n°4500785974 • Kick-off Meeting of the project - January 2010 PARIS (Philippe BOURIN, Mélanie GADELORGE, Sandrine FLEURY, CAPPELLESSO) • Congress MSC TOULOUSE 17/11/2010 (Sandrine FLEURY) • Congress ISCT Italy 10-14/09/2010 (Philippe BOURIN)
WP4	Travel cost	1204.00	• Bone Tec 2010 in Hannover (Nathalie CHEVALIER and Laura COQUELIN) • Congress MSC Toulouse Nov 2010 (Nathalie CHEVALIER and Julie LEOTOT)
TOTAL DIRECT COST		**377589.34**	
Indirect cost		113 276.80	*30% flat rate*
TOTAL COST		**490 866.14**	

Personnel, subcontracting and other major Direct cost items for Beneficiary 3 (BIOMATLANTE) for the period

Work Package	Item description	Amount (€)	Explanations
WP1	Personnel cost	54432.04	WP1 tasks: • 5 Engineers (Serge BAROTH, Pascal BORGET, Thomas MIRAMONT, Jeanne CHAMOUSSET ROMAN, Gaelle JOUAN; one during the whole year and four during the second half year) • 4 Assistants (Françoise MOREAU, Sophie DELHOMMEAU, Richard SERENNE, Jean-Baptiste SECHER) • Characterization density MBCP+/ Production MBCP+/Test of Cells and fluid absorption/Analysis and development of suspension Hydrogel/BCP/Providing MBCP+ and collagen materials to the different partners involved
WP1	Material cost	24974.97	• Deliveries of materials for others partners. In vitro culture cells with the material • Handling properties of the material
WP1	Other eligible cost	3179.04	• Fees for assitance for animals implantations • DHL - delivery products • Fees for assitance for animals implantations
WP1	Travel cost	517.48	• visit to CHU NANTES (Serge BAROTH) • visit to Polytech Nantes to analisys (Pascal BORGET) • notes of expenses INSERM Nantes – BIOMATLANTE (Guy DACULSI, Serge BAROTH and Pascal BORGET) • visit to CIC Bordeaux (Serge BAROTH)
TOTAL DIRECT COST		**83103.53**	
Indirect cost		16 620.71	*20% flat rate*
TOTAL COST		**99 724.23**	

Personnel, subcontracting and other major Direct cost items for Beneficiary 4 (CEA) for the period			
Work Package	**Item description**	**Amount (€)**	**Explanations**
WP4	Personnel cost	5132.65	WP4 tasks: • 1 searcher (Nathalie ROUAS FREISS) • 1 technician (Chantal SCHENOWITZ)
WP4	Other eligible cost	2614.00	• Lab consumables and chemical materials implantations
TOTAL DIRECT COST		**7746.65**	
Indirect cost		3 929.04	*76.55% flat rate for permanent personnel and 74.28% for non permanent personnel*
TOTAL COST		**11 675.69**	

Personnel, subcontracting and other major Direct cost items for Beneficiary 5 (POLICLINICO) for the period			
Work Package	**Item description**	**Amount (€)**	**Explanations**
WP2	Personnel cost	46600.00	WP2 tasks: • 1 Technical Director-Scientific supervision (Rosaria GIORDANO) • 1 R&D director-Scientific supervision (Lorenza LAZZARI) • 1 senior researcher (Experiment planning and execution (GMP production validation)) (Montemurro TIZIANA) • 1 junior researcher (Technical execution (GMP production): production protocol validation, reagent validation, data reporting) (Barbara BALUCE)
WP3	Personnel cost	43600.00	WP3 tasks: • 1 Technical Director-Scientific supervision (Rosaria GIORDANO) • 1 R&D director-Scientific supervision (Lorenza LAZZARI) • 1 senior researcher (Experiment planning and execution (GMP quality control validation)) (Andriolo GABRIELLA) • 1 junior researcher (Experiment execution (GMP quality control): flow cytometry, real time PCR analysis for senescence markers) (Viganò MARIELE)
WP4	Personnel cost	4000.00	WP4 tasks: • 1 junior researcher (Experiment execution (real time PCR analysis for differentiation markers)) (Vigano MARIELE)
WP7	Personnel cost	6600.00	WP7 tasks: • 1 technical director (scientific supervision) (Rosaria GIORDANO)
WP3	Other eligible cost	7036.64	• Antibodies (Flow cytometry analysis of MSC) • Mycoplasma kit (Mycoplasma testing of MSC)

WP4	Other eligible cost	1707.75	• Quantitative telomerase (Evaluation of senescence in MSC by QRT PCR) • RNA Extraction kit (QRT PCR to evaluate MSC differentiation properties) • Permeabilization Buffer (Flow cytometry analysis of MSC) • Primers (QRT PCR to evaluate MSC differentiation properties) • PCR reagent (QRT PCR to evaluate MSC differentiation properties)
WP2	Material cost	24627.28	• Medium • FBS • Cytokine • -> MSC production
WP3	Travel cost	814.07	• 2nd REBORNE Executive Committee Meeting (Rosaria GIORDANO)
TOTAL DIRECT COST		**134985.74**	
Indirect cost		26 997.15	*20% flat rate*
TOTAL COST		**161 982.89**	

Personnel, subcontracting and other major Direct cost items for Beneficiary 6 (CHU Nantes) for the period

Work Package	Item description	Amount (€)	Explanations
WP6	Personnel cost	44379.55	WP6 tasks: • 2 Hospital Assitant Contract employee (Pierre CORRE, Pascal HUET) • 1 University Hospital Professor (Jacques-Marie MERCIER) • 3 Hostital Practitioner (Jean-Philippe PERRIN, Elizabeth CASSAGNAU, Marie GAYET) • 1 University Hospital Teacher (Alain HOORNAERT) • 1 Hospital Engineer Contract employee (Véronique LE GAC)
WP7	Personnel cost	1370.28	WP7 tasks: • 1 Hospital Assitant Contract employee (Reading of documents, answering to questions) (Pierre CORRE) • 1 Hospital Engineer Contract employee (Reading of documents, answering to questions) (Véronique LE GAC)
WP6	Other eligible cost	202.05	UBIQUS (translation)
WP6	Travel cost	421.02	• Kick-off meeting - 14-15/01/2010 (Pierre CORRE) • Executive committee meeting - 16/04/2010 (Pierre CORRE and Véronique LE GAC) • Executive committee meeting - 28/09/2010 (Véronique LE GAC)
TOTAL DIRECT COST		**46372.9**	
Indirect cost		27 823.74	*60% flat rate*
TOTAL COST		**74 196.64**	

Personnel, subcontracting and other major Direct cost items for Beneficiary 7 (AP HP) for the period			
Work Package	**Item description**	**Amount (€)**	**Explanations**
WP5	Personnel cost	4965.17	WP5 tasks: • 1 researcher (experimental surgery creation of experimental model of osteonecrosis) (Yasuhiro HOMMA)
WP5	Other eligible cost	19500.00	• Small materiel for surgery, histology, animals (minipigs), bibliography… • -> Creation of experimental of osteonecrosis
TOTAL DIRECT COST		**24465.17**	
Indirect cost		14 679.10	*60% flat rate*
TOTAL COST		**39 144.27**	

Personnel, subcontracting and other major Direct cost items for Beneficiary 8 (KITOZYME) for the period			
Work Package	**Item description**	**Amount (€)**	**Explanations**
WP1	Personnel cost	33984.74	WP1 tasks: • 1 D&D Manager (Scientific management of the project, Implementation of the R&D work plan and follow-up of the specific tasks including the development of injectable bone substitutes and resorbable composites. Supervision of the technician (redaction of protocol, work plan , collect and supervision of the results) . Interactions and participation to meeting with other partners within the consortium. Writing of scientific and activity reports.) (Véronique MAQUET) • 1 Business Dev Manager (Administrative + scientific management of the project (Revision of the Consortium agreement, preparation of MTA for the transfers of samples to the other partners of the consortium); global supervision of the project, valorization of the results and IP management) (Sandrine GAUTIER) • 1 Technician (Laboratory work: preparation of a series of hydrogels composed of chitosan using different cross-linking strategies (both physical and chemical cross-linking). Characterization of gels including gelation time, gel hardness, gel stability in contact with culture medium, (rheology, pH, osmoloarity,…). Preparation of osteoinductive composites made of chitosan gels and CaP granules, Redaction of internal reports. Preparation of samples to be evaluated by other partners within the consortium) (Sylvia

			LEGRAIN) • Centrifugeuse (Purification and extraction of ultra-pure chitosan. Chitosan used is this project need to be of an ultra-pure grade.) • Sterilization Tests
WP1	Other eligible cost	13453.72	• Lab materials • Chemicals • Consultance Medical Device • Viscosimeter repair • Osmometer rent
WP1	Travel cost	498.00	Meeting Reborne Paris (Véronique MAQUET)
TOTAL DIRECT COST		**47936.46**	
Indirect cost		28 761.87	*60% flat rate*
TOTAL COST		**76 698.33**	

Personnel, subcontracting and other major Direct cost items for Beneficiary 9 (XPAND) for the period

Work Package	Item description	Amount (€)	Explanations
WP1	Personnel cost	98547.00	WP1 tasks: • 1 senior scientist (Project management, development of materials) (Florence de GROOT) • 1 scientist (research on novel materials, in vitro investigations) (Noël DAVIDSON)
WP1	Other eligible cost	11679.99	• R&D cost not included under materials/supplies major cost items
TOTAL DIRECT COST		**110226.99**	
Indirect cost		66 136.19	*60% flat rate*
TOTAL COST		**176 363.18**	

Personnel, subcontracting and other major Direct cost items for Beneficiary 10 (UPC) for the period

Work Package	Item description	Amount (€)	Explanations
WP1	Personnel cost	60085.22	WP1 tasks: • 5 researchers (Maria Pau GINEBRA MOLINS, Jose Maria MANERO PLANELLA, Emiliano SALVAGNI, Montserrat ESPAÑOL PONS, Daniel RODRIGUEZ RIUS)
WP7	Personnel cost	2110.70	WP7 tasks: • 1 Researcher (Maria Pau GINEBRA MOLINS)
WP1	Other eligible cost	5098.58	• Lab materials and consumables
WP1	Subcontracting cost	15477.37	• Fundació Bosch i Gimpera • Universitat de Barcelona
WP3	Travel cost	1693.56	• Congress ESB 2010, Tampere-Helsinki (Daniel RODRIGUEZ RIUS) • Paris Kick-off meeting Reborne Project (Noelia APARICIO BADENAS, Maria Pau

		GINEBRA MOLINS) • Executive Committee Meeting Paris (September 2010) (Maria Pau GINEBRA MOLINS)
TOTAL DIRECT COST	**84465.43**	
Indirect cost	78 880.94	*114.34% flat rate*
TOTAL COST	**163 346.36**	

Personnel, subcontracting and other major Direct cost items for Beneficiary 11 (UAM) for the period

Work Package	Item description	Amount (€)	Explanations
WP5	Personnel cost	44801.19	WP5 tasks: • 4 professors (coordinator, clinical protocol developmment, haematology protocol, patient selection) (Enrique GOMEZ BARRENA, Eduardo GARCIA CIMBRELO, Angela FIGUERA, Jose CORDERO) • Paris 14-17/01/2010 KICKOFF MEETING (Manuel Nicolas FERNANDEZ RODRIGUEZ, Enrique GOMEZ BARRENA) • Paris Executive Committee Meeting April 2010 (Enrique GOMEZ BARRENA) • Paris Executive Committee Meeting September 2010 (Enrique GOMEZ BARRENA) • Toulouse 18-21/11/2010 WP2 AND 5 MEETING (Manuel Nicolas FERNANDEZ RODRIGUEZ)
WP5	Travel cost	3954.71	
TOTAL DIRECT COST		**48755.9**	
Indirect cost		29 253.54	*60% flat rate*
TOTAL COST		**78 009.44**	

Personnel, subcontracting and other major Direct cost items for Beneficiary 11 Third Party (UAM) for the period

Work Package	Item description	Amount (€)	Explanations
WP2	Personnel cost	7644.07	WP2 tasks: • 1 principal investigator (Manuel Nicolas FERNANDEZ RODRIGUEZ) • 3 Researchers (Rosa Mª GONZALO DAGANZO, Rocío SANCHEZ RUIZ, Trinidad MARTIN DONAIRE, Enrique GOMEZ BARRENA)
WP2	Other eligible cost	4983.38	• Fungible goods
WP2	Travel cost	787.70	Mad-Nantes-Mad Ticket Airlines [General Assembly of the European REBORNE project on January 31st and February 1st 2011 U.of Nantes]

		(paid in December 2010) (Rosa Mª GONZALO DAGANZO)
TOTAL DIRECT COST	**13415.15**	
Indirect cost	8 049.09	*60% flat rate*
TOTAL COST	**21 464.24**	

Personnel, subcontracting and other major Direct cost items for Beneficiary 12 (UNIMORE) for the period

Work Package	Item description	Amount (€)	Explanations
WP4	Personnel cost	68266.60	WP4 tasks: • 1 assistant professor (Massimo DOMINICI) • 2 full professors (Paolo PAOLUCCI, Pierfranco CONTE) • 1 laboratory technician (Luigi CAFARELLI)
WP7	Personnel cost	4580.40	WP7 tasks: • 1 assistant professor (Massimo DOMINICI) • 1 full professor (Paolo PAOLUCCI) • -> writing protocols for ethical clearance; Contributing to deliverables
WP4	Material Cost	20142.36	• BD FACSARIA III 2 Laser: 6 Blue/2 Red con ACDU - FACSARIA WORKSTATION HP XW4600 - 19" NEC LCD 191M - STAMPANTE XEROX 8560N Phaser - FACSARIA TABLE
WP4	Other eligible Cost	26330.82	• lab materials and consumables mainly for cell culture
WP4	Travel cost	5237.24	• Osteonecrosis Meeting 23-27 Jan 2010 - Washington - USA (Massimo DOMINICI) • Reborne Kick-off Meeting 12-15 Jan 2010 Paris-(Massimo DOMINICI) • Reborne first executive committee meeting 15-20 April 2010 Paris - (Massimo DOMINICI) • Reborne Meeting 28 September 2010 - PARIS - (Massimo DOMINICI) • Reborne Meeting 17-20 November 2010 - Toulouse- France (Massimo DOMINICI) • Meeting Reborne 30 November 2010 Milano (Massimo DOMINICI)
TOTAL DIRECT COST		**124557.42**	
Indirect cost		74 734.45	*60% flat rate*
TOTAL COST		**199 291.87**	

Personnel, subcontracting and other major Direct cost items for Beneficiary 13 (UMFTVB) for the period			
Work Package	**Item description**	**Amount (€)**	**Explanations**
WP7	Personnel cost	24524.50	WP7 tasks: • 5 technical scientifics (Carmen BUNU, Cristina DRAGOMIRESCU, Daciana NISTOR, Carmen PITIC, Carmen TATU)
WP5	Travel cost	1218.80	• Paris - REBORNE kick-off meeting, January 2010 (Tatu Fabian Romulus)
WP7	Travel cost	5282.98	• Paris - First REBORNE meeting - 15-16 April 2010 (Carmen BUNU) • Bucharest - meeting with the Romanian Medical National Ethics Committee representative for promoting REBORNE project at national level - 7-11 may 2010 (Carmen BUNU) • Madrid-meeting with Enrique Gomez Barrena, coordinator of WP5, to discuss details of the legal issues for the first orthopaedic clinical trial, and to set up the procedures for CRO call for tender (Carmen BUNU) • Bucharest-consultation with Ethical Committee regarding the REBORNE project (Carmen BUNU) • Paris, REBORNE Executive Committee meeting April 2010 (Carmen BUNU) • Paris, REBORNE Executive Committee meeting September 2010 (Carmen BUNU) • Toulouse-1st European Conference on Mesenchymal Stem Cells (Carmen BUNU, Gabriela TANASIE, Florina BOJIN)
WP7	Other eligible Cost	511.64	paper towels, toner, paper, cartridges ->hygiene and cleaning materials, preparation of documents
TOTAL DIRECT COST		**31537.92**	
Indirect cost		6 307.58	*20% flat rate*
TOTAL COST		**37 845.51**	

Personnel, subcontracting and other major Direct cost items for Beneficiary 14 (CHU Tours) for the period			
Work Package	**Item description**	**Amount (€)**	**Explanations**
WP5	Personnel cost	1643.68	WP5 tasks (Philippe ROSSET)
TOTAL DIRECT COST		**1643.68**	
Indirect cost		328.74	*20% flat rate*
TOTAL COST		**1 972.42**	

Personnel, subcontracting and other major Direct cost items for Beneficiary 15 (UNITUE) for the period			
Work Package	**Item description**	**Amount (€)**	**Explanations**
WP4	Personnel cost	57226.10	WP4 tasks: • 1 scientist (PhD) (Preparation of animal testing licence and ethics proposal for the use of human material in animal experiments, Establishment of mouse transplantations and follow up/ Collection of human stem cells for usage in animal experiments, Mouse follow up/ Mouse transfer to Uulm/ Collection of human stem cells for usage in animal experiments, Mouse follow up/ Mouse transfer to Uulm/ Collection of human stem cells for usage in animal experiments) (Annika ERBACHER)
WP4	Other eligible cost	28940.28	• Plasticware • Antibodies • Cell Culture Products/Chemicals • Laboratory Animals • Other Consumables
WP4	Travel cost	418.89	REBORNE Meeting January 2010 Paris (Ingo MÜLLER)
TOTAL DIRECT COST		**86585.27**	
Indirect cost		51 951.16	*60% flat rate*
TOTAL COST		**138 536.44**	

Personnel, subcontracting and other major Direct cost items for Beneficiary 16 (UULM) for the period			
Work Package	**Item description**	**Amount (€)**	**Explanations**
WP2	Personnel cost	19161.44	WP2 tasks: • 2 MTAs (MSC expansion, platelet lysate production) (Sarah CHESTER, Karin FUCHS) • 1 PhD (MSC expansion; MSC characterization) (Alexander ERLE) • 1 postdoctoral fellow (Coordination of MSC expansion) (Markus ROJEWSKI) • 1 project leader, medical director (Management, Design of GMP expansion protocols; bone marrow aspiration of healthy donors) (Hubert SCHREZENMEIER)
WP3	Personnel cost	19161.44	WP3 tasks: • 1 master thesis (MRI scanning of labelled MSC; MSC - Biomaterial interaction) (Ariane BRUCHE) • 2 technicians (MSC expansion and MSC characterization) (Gisela BAUR, Thomas BECKER) • 2 MTAs (MSC - biomaterial interaction and MSC expansion) (Sarah CHESTER, Karin FUCHS) • 1 PhD (MSC characterization; MSC biomaterial interaction) (Alexander ERLE) • 1 Project leader, medical director (Management, Design of experiments; MRI scanning) (Hubert SCHREZENMEIER)
WP4	Personnel cost	31868.15	WP4 tasks: • 1 Project Leader, Head of Institute (Management) (Anita IGNIATIUS) • 1 postdoctoral research fellow (Ronny BINDL) • 1 Med. Documentalist (Brigitte SIEGEL) • 2 PhDs (R&D Activities) (Anna Elise RAPP, Ina VERNIKOUSKAYA) • 1 Project Leader (R&D Activities, Management) (Volker RASCHE)
WP2	Other eligible cost	13421.83	Laboratory consumables and materials
WP4	Other eligible cost	41632.79	Laboratory materials
WP2	Travel cost	147.06	Project meeting Toulouse, 17. - 21.11.2010 (Hubert SCHREZENMEIER)
WP5	Travel Cost	650.74	Project Meeting Paris, 13. - 15.01.2010 (Christian EHRNTHALLER)
TOTAL DIRECT COST		**126043.45**	
Indirect cost		75 626.07	*60% flat rate*
TOTAL COST		**201 669.51**	

Personnel, subcontracting and other major Direct cost items for Beneficiary 17 (UNIVR) for the period			
Work Package	**Item description**	**Amount (€)**	**Explanations**
WP2	Personnel cost	12668.85	WP2 tasks: • 1 assistant professor (organization and coordination of the immunological experiments; supervision in the execution of standardization experiments ; data analysis and interpretation; organization of periodical meetings in the LAB) (Mauro KRAMPERA) • 1 full professor (support to organization and coordination of the experiments; data analysis and interpretation) (Giovanni PIZZOLO)
WP3	Personnel cost	5404.48	WP3 tasks: • 1 assistant professor (organization and coordination of the immunological experiments; supervision in the execution of standardization experiments ; data analysis and interpretation; organization of periodical meetings in the LAB) (Mauro KRAMPERA) • 1 full professor (support to organization and coordination of the experiments; data analysis and interpretation) (Giovanni PIZZOLO)
WP4	Personnel cost	3101.06	WP4 tasks: • 1 associate professor (Patient's selection, Analysys of Patient's data, Organization of clinical phase) (Daniele DE SANTIS) • 1 full professor (Patient's selection, Analysys of Patient's data, Organization of clinical phase) (Pierfrancesco NOCINI)
WP2	Other eligible cost	29260.95	Laboratory materials and consumables (reagents for the experiments aimed at the standardization of the immunological assays to characterize the immune regulatory properties of mesenchymal stem cells of different origin)
TOTAL DIRECT COST		**50435.34**	
Indirect cost		30 261,21	*60% flat rate*
TOTAL COST		**80 696,55**	

Personnel, subcontracting and other major Direct cost items for Beneficiary 18 (ALCIMED) for the period			
Work Package	**Item description**	**Amount (€)**	**Explanations**
WP0	Personnel cost	29812.72	WP0 tasks: • 1 Project manager (Nadège PENHALEUX) • 3 consultants (Florian LIBERAL, Manon GIOAN, María RODRIGUEZ, Loïc MARCE) Management of the project, reporting and organisation of meetings Elaboration of the due deliverables
WP7	Personnel cost	10475.13	WP7 tasks: • 4 consultants (Rutger MANTINGH, Dorothée HANAUT, Loïc Marcé, Maria RODRIGUEZ) • Parking Kick-off REBORNE (15/01/2010) (Nadège PENHALEUX) • Lunch for all partners attending the Executive Committee meeting 1 (16/04/2010) (Nadège PENHALEUX) • Lunch meeting REBORNE (20/04/2010) (Nadège PENHALEUX) • Lunch for all partners attending the Executive Committee meeting 2 (28/09/2010) (Nadège PENHALEUX)
WP0	Other eligible cost	522.85	
TOTAL DIRECT COST		**40810.7**	
Indirect cost		58 981.41	*Simplified method*
TOTAL COST		**99 792.11**	

Personnel, subcontracting and other major Direct cost items for Beneficiary 19 (UiB) for the period			
Work Package	**Item description**	**Amount (€)**	**Explanations**
WP6	Personnel cost	26230.77	• 1 Professor emeritus (planning the first maxillofacial clinical trial, doing the necessary contacts with the personnel and departments involved in the first clinical trial, recruiting patients and preparing the application for the ethical clearance from the local authority in Bergen.
WP6	Travel Cost	2132.58	Travel to Toulouse 18/11-21/11 2010 (Solve HELLEM, Mustafa KAMAL, Kristina F. ARVIDSON)
TOTAL DIRECT COST		**28363.35**	
Indirect cost		17 018.01	*60% flat rate*
TOTAL COST		**45 381.36**	

Personnel, subcontracting and other major Direct cost items for Beneficiary 20 (UMC Utrecht) for the period			
Work Package	**Item description**	**Amount (€)**	**Explanations**
WP6	Personnel cost	4666.71	WP6 tasks: • 1 head of department (Ronald KOOLE) • 1 post doc (AP de RUITER) • 1 PhD candidate (Nard G. JANSSEN) • 2 researchers (A van der BILT, J ABBINK) • (publications, training Cone Beam CT-A/B; training Cone Beam CT-A/B, research)
WP6	Travel cost	615.00	Training 'Cone Beam CT course A' (October 25, 2010) (Nard G. JANSSEN)
TOTAL DIRECT COST		**5281.71**	
Indirect cost		3 169.03	*60% flat rate*
TOTAL COST		**8 450.74**	

Personnel, subcontracting and other major Direct cost items for Beneficiary 21 (IOR) for the period			
Work Package	**Item description**	**Amount (€)**	**Explanations**
WP5	Personnel cost	8410.81	WP5 tasks: • 2 MDs (Management and internal coordination of the project, dissemination activities, meetings) (Nicola BALDINI, Donatella GRANCHI) • 1 biologist (Gabriela CIAPETTI) • 1 biotechnologist (activity planning, testing, meetings) (Donatella GRANCHI) • 1 coordinator (Administrative management and coordination of the project) (Lucia SCIOSCIA)
WP5	Other eligible cost	1043.36	• Various diagnostics and reagents and other consumables
WP5	Travel cost	1859.11	Kick-off Meeting - University of Nantes (PARIS) - 14-15/01/2010 (Francesca PERUT, Gabriela CIAPETTI, Nicola BALDINI)
TOTAL DIRECT COST		**11313.28**	
Indirect cost		8 011.28	*95.24% rate for personnel cost only*
TOTAL COST		**19 324.56**	

Personnel, subcontracting and other major Direct cost items for Beneficiary 22 (MPG) for the period			
Work Package	**Item description**	**Amount (€)**	**Explanations**
WP1	Personnel cost	77402.74	WP1 tasks: • 4 PhD students Synthesis / production of nanocapsules Isothermal titration of synthesized nanocapsules Microscopy analysis of synthesized nanocapsules Release studies of synthesized nanocapsules
WP1	Travel cost	409.23	Reborne Kick-off Meeting Paris (Völker MAÏLANDER)
WP1	Other eligible cost	14.38	UPS Shipping cost. Original hardcopy documents for the first reporting period 01/01/2010-30/06/2010 to the Reborne Coordinator.
TOTAL DIRECT COST		**77826.35**	
Indirect cost		108 750.85	*140.5% flat rate*
TOTAL COST		**186 577.20**	

Personnel, subcontracting and other major Direct cost items for Beneficiary 23 (AOU MEYER) for the period			
Work Package	**Item description**	**Amount (€)**	**Explanations**
WP5	Personnel cost	8880.00	WP5 tasks: • 1 Consultant (Contacts with phisicians, Competent Authorities and Ethics Committee; documents and protocol evaluation and review; administrative reports.) (Irene SPITALERI)
TOTAL DIRECT COST		**8880.00**	
Indirect cost		5 328.00	*60% flat rate*
TOTAL COST		**14 208.00**	

Personnel, subcontracting and other major Direct cost items for Beneficiary 24 (ULG PARO) for the period			
Work Package	**Item description**	**Amount (€)**	**Explanations**
WP6	Personnel cost	2475.37	WP6 tasks: • 1 chief of clinic (Geoffrey LECLOUX) • first reborne annual meeting , work on experiment protocol
WP6	Travel cost	572.00	• First annual meeting (Geoffrey LECLOUX)
TOTAL DIRECT COST		**3047.37**	
Indirect cost		1 828.42	*60% flat rate*
TOTAL COST		**4 875.79**	

3.5 Deliverables and milestones tables

3.5.1 Deliverables

Del n°	Deliverable name Version	WP N°	Lead Beneficiary	Nature	Dissemination Level	Delivery date from Annex I (proj month)	Delivered Yes/No	Actual/Forecast delivery date	Comments
0. 1	Consortium Agreement	0/99	18	R	CO	0	NO	16	Currently in procedure of signature, delay due to multiple modifications demanded by partners
0.3	First yearly periodic report: progress of the work, use of resources and financial statement	0/99	18	R	CO	12	YES	14	
0.10	Governing Board meeting report	0/99	18	R	CO	0	YES	9	Kick-Off meeting held in Paris in Jan 2010 – The deliverable was finished on due date but the submission to ECAS has been delayed
0.11	Governing Board meeting report	0/99	18	R	CO	12	YES	15	Governing Board meeting report was held in Nantes on the 31st of January and 1st of February 2011 in Nantes, the deliverable was finished 3 weeks later and then the due time for all partners to read and comment it was respected
0.26	Internal Communication Tools	0/99	18	0	CO	3	YES	14	The deliverable was finished on due date but the submission to ECAS has been delayed

0.16	Executive Committee meeting report	0/99	18	R	CO	4	YES	14	The deliverable was finished on due date but the submission to ECAS has been delayed
0. 2	Internal Financial Template	0/99	18	R	CO	5	YES	9	The deliverable was finished on due date but the submission to ECAS has been delayed
0.17	Executive Committee meeting report	0/99	18	R	CO	8	YES	14	The deliverable was finished on due date but the submission to ECAS has been delayed
0. 3	First yearly periodic report: progress of the work, use of resources and financial statement	0/99	18	R	CO	12	YES	14	
0.11	Governing Board meeting report	0/99	18	R	CO	12	NO	15	Drafted and in validation process
1.1	Selection of most suitable biomaterial for first orthopaedic clinical study	1	3	R	CO	9	YES	11	The deliverable was finished on due date but the submission to ECAS has been delayed
1.2	Report on physico-chemical and biological properties of CaP granules for supporting MSCs	1	3	R	CO	12	YES	14	This deliverable involved many partners and the slight delay is due to the exchange of information

1.3	Delivering a packaging device for association of CaP ceramics granules for with cells	1	3	P	CO	12	YES	14	The deliverable was finished on due date but the submission to ECAS has been delayed
1.4	Report on osteogenic properties of CaP ceramics and cells constructs in small animal models with various cell sources, doses and osteogenic conditions	1	1	R	CO	12	YES	14	
2. 1	Definition of PGFEP preparation	2	2	R	CO	3	YES	9	The delay is due to the SOP; preparation type was conceived on time.
2. 2	SOP for culture of BM-MSC and ASC	2	2	R	CO	6	YES	14	D2.2 had been delivered late because the experimentations had been delayed in some partner laboratory due to the availability of the raw material : the bone marrow that come from human donors.

2. 3	SOP for culture of FB-MSC	2	5	R	CO	9	YES	14	A slight delay due both to administrative issues related to the transferring of the grant at the different Institutions involved in REBORNE and to the important interdependence of this WP from the other WP.
2. 4	Production of cells for the first clinical trial	2	2	P	CO	12	NO		This deliverable cannot be delivered as the clinical trials have not started yet
3. 1	Validated protocols for QC on the genotypic stability and phenotypic profile of BM and AT MSC	3	2	R	CO	9	NO	15	This deliverable is drafted but some points are under discussion
3. 2	Validated protocols for QC on BM and AT MSC /biomaterials combination	3	5	R	CO	12	YES	14	

4.4	Report standardized animal MSC isolation and culture protocols	4	12	R	CO	6	YES	10	The delay is due to administrative issues impacting RTD activities (UNIMORE received subvention in April 2010). In some cases (i.e Rabbit and mini-pig marrow sources) it has been difficult to finalize the experiments, therefore more work and time was required, this is also stated in the annual report of WP4. In any case this delay is having or will have an impact on the tasks 4, 5, 6 of WP4.
4.1	Provide improved potency assays of bone regeneration for GMP manufactured MSC and biomaterials	4	12	R	CO	9	YES	14	The experiments using GMP produced cells in combination with biomaterials have started in September 2010 and could not begin before as SOP for production were not standardized. 7 batches of 100 million cells from UULM #16 have been implanted and 4 series have been analyzed by INSERM #1. Report is in preparation.
4.2	Provide standardized diagnostic *in vivo* and post-mortem read-out of bone re-growth	4	1	R	CO	12	YES	14	*In vivo* read out of bone formation with alive animals have been done but it is not possible to distinguish bone from biomaterial by using µCT. The post mortem read out is possible. Report is in preparation at INSERM #1

4.7	Identify cell combinations and *in vitro* conditions to support angio-osteogenesis	4	2	D	CO	12	YES	14	As for 4.1 with no impact in project prosecution
4.10	Identify proper cultures conditions enhancing immunomodulatory properties of MSC	4	2	D	CO	12	YES	14	As for 4.1 with no impact in project prosecution
7. 1	REBORNE WP7 Action Plan	7	13	R	CO	2	YES	9	The deliverable was finished on due date but the submission to ECAS has been delayed
7. 2	Listing of local / regional / national ethics committees in the countries of teams involved in REBORNE	7	13	R	PU	3	YES	9	The deliverable was finished on due date but the submission to ECAS has been delayed
7. 3	Listing of local / regional / national regulatory authorities in the countries of teams involved in REBORNE	7	13	R	PU	3	YES	9	The deliverable was finished on due date but the submission to ECAS has been delayed
7. 4	REBORNE Exploitation guidelines	7	18	R	CO	3	YES	15	The deliverable was drafted in month 5, but its submission was delayed by a slow internal validation process

7. 5	Report on legal framework on preclinical trials involving animal use	7	13	R	CO	4	YES	9	The deliverable was finished on due date but the submission to ECAS has been delayed
7. 6	Report on approval procedure and core submission package for regulatory authorities for preclinical trials	7	13	R	CO	4	YES	14	The deliverable has been delayed mostly due to some delays in the internal validation process
7. 7	REBORNE Plan for Using and Disseminating Knowledge	7	18	R	CO	4	YES	14	The deliverable was finished on due date but the submission to ECAS has been delayed
7. 8	Report on review and voting procedure and core submission package for Ethical committees for preclinical trials	7	13	R	CO	6	YES	9	The deliverable was finished on due date but the submission to ECAS has been delayed
7. 9	Report on current status of ethical issues in the EU and world-wide, as well as in the countries of teams involved in the project	7	13	R	PU	6	YES	9	The deliverable was finished on due date but the submission to ECAS has been delayed

7.10	Website dedicated to the REBORNE project	7	18	O	PU	6	YES	6	
7.11	Report on legal framework on harvesting, banking and use of human MSC	7	13	R	PU	9	YES	9	
7.12	Report on ethical issues for harvesting, banking and use of human MSC.	7	13	R	PU	9	YES	9	
7.13	Report on approval procedure and core submission package for regulatory authorities for clinical trials	7	13	R	CO	9	YES	9	
7.14	Report on review and voting procedure and core submission package for Ethical committees for clinical trials	7	13	R	CO	12	YES	9	

7.15	Report on legal framework on clinical trials involving human subjects treated with MSC and biomaterials	7	13	R	PU	12	YES	9	
7.16	First annual report of the Ethical advisory board	7	13	R	CO	12	YES	14	This deliverable was written in the postpone of the Government Board Meeting in Nantes

3.5.2 Milestones

Milestone no.	Milestone name	Work package no	Lead beneficiary	Delivery date from Annex I Dd/mm/yy	Achieved Yes/No	Actual / Forecast achievement date Dd/mm/yy	Comments
0.1	Kick-off meeting	0	1	31/01/2010	YES	14-15/01/2010	-
0.2	Annual meetings	0	1	31/12/2010	YES	31/01/2011-1/02/2011	-
0.3	Executive Committee meetings	0	1	30/04/2010 and 31/08/2010	YES	16/04/2010 and 28/09/2010	-
1.1	Selection of biomaterials for long bone dyaphyseal fractures clinical trials	1	10	01/12/2010	YES	01/12/2010	-
1.4	Selection of biomaterials for premaxillary vertical bone augmentation clinical trials	1	10	31/12/2010	YES	01/12/2010	-

3.1	Selection of validated tests to be used for QC on the genotypic stability and phenotypic profile of BM and AT	3	2	30/06/2010	YES	15/02/2011	achieved but the deliverable is under discussion
3.5	Selection of validated tests to be used for QC on MSC-biomaterials combination	3	16	31/12/2010	NO	30/06/2011	The standard operating procedures for producing clinical lots of hMSC has been defined in January 2011. Consequently, the definition of quality controls for MSC-biomaterial combination could not be completed although some preliminary research activities have been done. This milestone is planned to be delivered in the first half of 2011.
4.1	Potency assays to be transferred into WP3	4	12	30/09/2010	YES	01/02/2011	-
4.2	Standardized animal MSC isolation procedures	4	12	30/06/2010	YES	01/09/2010	-
4.3	Standardized assays for bone regeneration *in vivo*	4	1	31/12/2010	YES	01/02/2011	-

4.4	Optimization bone regeneration conditions based on biomaterials and cGMP grade MSC	4	1	31/12/2010	NO	30/06/2011	Under progress in parallel to D4.3 due for June 2011
4.6	Establishment of pro-angiogenic conditions for bone regenerations	4	1	31/12/2010	NO	31/12/2011	D4.7 delivered but the milestone is under progress in parallel with the D4.5 and D4.6
4.7	Allogeneic MSC as valuable tools for bone regenerations	4	16	31/12/2010	NO	31/12/2011	Under progress in parallel with D4.11, D4.12 and D4.13
4.8	Establishment of animal models of bone regeneration in FHO	4	12	31/12/2010	NO		Under progress
4.9	Establishment of animal model of bone regeneration in maxillo-facial defects	4	1	31/12/2010	NO		Under progress, 2 models have been developed calvaria in nude mice, maxillary defect in rabbits
4.10	Establishment of animal model of bone regeneration in long-bone defects	4	2	31/12/2010	NO		Under progress in parallel with D4.16
7.1	Ethics, legal and regulatory issues on	7	13	30/06/2010	YES	01/06/2010	-

	preclinical trials						
7.2	Ethics, legal and regulatory issues on clinical trials	7	13	31/12/2010	YES	01/12/2010	-
7.3	Ethics, legal and regulatory issues on harvesting/banking and use of human MSC	7	13	31/12/2010	YES	01/06/2010	-
7.6	Annual workshops	7	1	31/12/2010	YES	31/01/2011	-

Attachments

- Attachment 1: Ortho 1 protocol
- Attachment 2: Maxillo 1 protocol
- Attachment 3: Official documents justifying the modification of partner #17 UNIVR
- Attachment 4: Official documents justifying the modification of partner #5 POLICLINICO
- Attachment 5: Official documents justifying the legal situation of partner #11 UAM
- Attachment 6: Form Cs Summary

Attachment 1: Ortho 1 protocol

Institut thématique
Santé publique
Pôle Recherche Clinique

Institut national
de la santé et de la recherche médicale

BIOMEDICAL RESEARCH PROTOCOL

Evaluation of efficacy and safety of autologous MSCs combined to biomaterial to enhance bone healing in patients with delayed consolidation after long bone fracture requiring graft apposition or alternative orthobiologics.

Short title: OrthoCT 1 REBORNE

Sponsor N°	EudraCT N°
ORTHO1	2010-024257-37

DRAFT V6, 09/03/2011
FINAL VERSION: JJ/MM/AAAA

CONFIDENTIAL

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☐ **monocentre trial ;**
☒ **multicentre trial**

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HISTORICAL VERSIONS OF THE PROTOCOL

Partie réservée au promoteur

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CI	Chief Investigator
CRA	Clinical Research Associate (Monitor)
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Clinical Trials
EC	Ethics Committee
GCP	Good Clinical Practice
GP	General Practitioner
IB	Investigators Brochure
ICF	Informed Consent Form
INSERM	Institut national de la santé et de la recherche médicale
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Products
IRB	Independent Review Board
MRI	Magnetic resonance imaging
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC/SPC	Summary of Products Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions

SYNOPSIS OF THE STUDY

Study Title	Evaluation of efficacy and safety of autologous MSCs combined to biomaterial to enhance bone healing in patients with delayed consolidation after long bone fracture requiring graft apposition or alternative orthobiologics.
EudraCT. no.	2010-024257-37
Clinical Phase	Interventional Phase II study
Trial Design	Prospective, multicenter Phase II interventional Clinical Trial to evaluate efficacy and safety
Trial Participants	Recruitment of 30 patients
Investigation centres	5 European centres/ 4 countries (2 centres in France, 1 in Spain, 1 in Germany, 1 in Italy)
Planned Sample Size	Total enrolment : 30 patients (about 6 / investigation centre)
Follow-up duration	6 months (24 weeks) after inclusion
Trial Period	24 months (12 months for enrolment, 6 months FU, 6 months analyses)
Primary Objective	To obtain clinical and radiological consolidation of diaphyseal and/or metaphysodiaphyseal fractures (femur, tibia, humerus) status delayed union (after 3 months) treated by standard care procedures plus apposition of biomaterial with autologous MSCs at the fracture site.
Primary Endpoint	Number of patients with proven bone healing at 6 weeks, 12 weeks, and 24 weeks (defined as 3 out of 4 or 2 out of 3 cortices with imaging confirmed bone bridging), in proportion of the recruited, treated patients.
Secondary Endpoints	*Efficacy endpoints:* -Radiological callus present at 6 weeks, 12 weeks, and 24 weeks. -Clinical consolidation at 6, 12, 24. -No reoperation done or scheduled at 24 weeks. *Safety endpoints:* -Local complication rate regarding the non-union treatment in the FU -Local and general complication rate regarding infections, or other effects of MSC in the FU of patients. *Other:* -Economical impact.
Investigational Medicinal Products	IMP to be described: CE marked material (granulated biphasic calcium phosphate by Biomatlante) plus pluripotential MSCs from bone marrow isolation, expanded under GMP protocol in associated facilities.
Form	Mixture of biomaterial and cells in surgical setting, according to protocol
Dose	$20x10^6$ cells per 1cc of biomaterial in 2 syringes of 5cc (total 10cc) per case in a single administration.
Route	Local administration in surgical procedure to treat non-union.
Control product	Literature definition of delay to clinical and radiological consolidation with autograft or with BMPs, and reoperation rate.
Analysis	Descriptive statistics will be estimated

TABLE OF CONTENTS

1. STUDY RATIONALE – HISTORICAL BACKGROUND

Context and Rationale.

Bone grafting is widely used in hospitals to repair injured, aged or diseased skeletal tissue. In Europe, about one million patients encounter a surgical bone reconstruction annually and the numbers are increasing due to our ageing population. Bone grafting intends to facilitate bone healing through osteogenesis (i.e. bone generation) at the site of damage, but this is only attained presently by including cells capable of forming bone into the augmentation. Other options to augment this bone repair include osteoinductive (i.e. bone inducers) and osteoconductive (i.e. bone guides) capabilities of the supplied coadjuvants to the surgical treatment of the lesion.

Bone autograft is the safest and most effective grafting procedure, since it contains patient's own bone growing cells (to enhance osteogenesis) and proteins (to enhance osteoinduction), and it providing a framework for the new bone to grow into (osteoconduction). However, bone autograft is limited in quantity (about 20 cc) and its harvesting (e.g. from the iliac crest) represents an additional surgical intervention, with frequent consequent pain and complications.

The next solution is allograft bone directly coming from tissue banks (fresh-frozen) or prepared to be conserved (dried or lyophilized). This solution does not contain living cells and some matrix proteins are destroyed by virus-inactivation treatment and freezing process, thus it only guarantees osteoconductive properties. Moreover, allograft bone may transfer disease or lead to immunological rejections [1].

Since both autograft and allograft have drawbacks, scientists have long searched for bio-compatible materials that could be used in place of the transplanted bone [1,2]. Although most of synthetic bone substitutes available possess some of the positive properties of autograft (particularly, osteoconductive capabilities and occasionally, osteoinductive properties), none yet have all the benefits of one's own bone (osteogenic properties). Basically and besides bone autografting, which is the only truly osteogenic material, orthobiological solutions today available to surgeons include osteoconductive and osteoinductive products, such as different preparations of bone allograft (fresh-frozen or dried by lyophylisation, warranting osteoconduction), different synthetic substitutes (with variable properties but particularly osteoconductive), and synthetic pharmaceuticals with osteoinductive properties (such

as bone morphogenetic proteins, BMPs). Available evidence confirms the outcome of fractures and non-unions treated by surgical techniques augmented by autograft [3] and by BMPs [4], thus this information may be compared to efficacy studies about other solutions.

In view of these limitations and the increasing number of bone grafting procedures, surgeons are looking for more advanced therapies such as tissue engineering [5]. Tissue engineering combines bone marrow cells or mesenchymal stem cells (MSCs), synthetic scaffolds and molecular signals (growth or differentiating factors) in order to form hybrids constructs. In a classical approach, bone tissue engineering consists of harvesting bone marrow from a patient, isolating MSCs by their adherence to tissue culture plastic, expanding and differentiating those cells in culture to a sufficient number and then seeding them onto a suitable synthetic scaffold prior to implantation into the same patient [6].

For bone reconstruction purposes, human MSCs have been seeded and cultured on porous calcium phosphate ceramics in osteogenic media (dexamethasone, ascorbic acid, β-glycerophosphate). Some clinical studies with low numbers of patients have been reported using this approach but the outcomes were inconsistent with low efficacy in bone regeneration [7-9]. The reasons of the limited clinical success may be due to several bottlenecks in the multidisciplinary field of bone tissue engineering:

- Biomaterials used as bone void fillers are inspired by the bone extracellular matrix (hydroxyapatite, collagen I) but need to be colonized by cells and vascularized in order to promote bone tissue formation and healing. The regenerative capabilities of current biomaterials are still limited to small bone defects.
- The autologous approach for isolation and osteogenic differentiation of MSCs is highly demanding in terms of logistics, production and safety of culture conditions leading to a costly therapeutic procedure.
- The selection of a restricted population of cells from different donors with age and genetic diversities remains a challenge for regenerative medicine at this early stage of research.
- The association of biomaterials and osteoprogenitor cells raises technical challenges (i.e. cell sources, types, doses, timing) and regulatory issues (devices with medicinal drugs) for the implementation of clinical trials.

- Moreover, bone formation requires different cell populations that cooperate to set up complex 3D tissue under the guidance of biomechanical cues while vascularization plays a major role in tissue healing.
- Osteogenic differentiation was only induced *in vitro* in the above mentioned trials, but was not supported by the release of osteogeneic factors *in vivo* by the graft itself. This could substantially improve the efficacy.

Major limb injury frequently related to accidents and multiple trauma patients are of marked interest in developed countries, where traffic accidents among others cause severe bone and joint injuries resulting in long treatments with substantial socioeconomic effects, as well as in less developed countries, where secondary complications generate frequent disabilities. Long bone fractures are difficult and slow to heal due to thick cortices callus formation and remodeling. These may require up to 12 months until consolidation is completed. Long treatments associate significant loss of working days, and economic effects on the patient and the society, and the risk of non-union and permanent disabilities related to malunion, joint stiffness, muscular atrophy, or reflex sympathetic dystrophy. Therefore, fracture healing in cases of delayed union or non-union remains a challenge where orthobiologics-based tissue engineering approach is the augmentation strategy to standard treatments as an alternative to bone graft [9]. In this challenge, the use of bone marrow autologous MSCs expanded in the adequate GMP facility and transported by bioceramics into the bone defect is a realistic solution, with significant basis on present knowledge and compliance with ethical principles [10].

Hypothesis

We hypothesize that using synthetic bone substitutes associated with autologous bone marrow cells differentiated into osteoblasts contribute to the resolution of the health and socioeconomic complications of delayed union or non-union after dyaphyseal and metaphysodyaphyseal fractures with efficacy and safety.

Expected results

The expected results are to obtain bone consolidation thus healing of delayed union or non-union, as proven by imaging techniques, without using bone graft. This will prove the efficacy of the proposed IMP based on the granulated biphasic calcium

phosphate with pluripotent MSCs expanded in a GMP facility and mixed in the surgical setting 1 hour before implantation. No expected complications related to the procedure are expected. Changes in serum levels of bone turnover markers will be described. Economical impact is expected to be limited.

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2 OBJECTIVES

2.1 Primary Objective

To obtain consolidation, without increasing the complication rate, of diaphyseal and/or metaphysodiaphyseal fractures (femur, tibia, humerus) status delayed union (after 3 months) treated by standard care procedures plus apposition of biomaterial with autologous MSCs at the fracture site.

2.2 Primary Endpoint

Proven bone healing at 6 weeks, 12 weeks, and 24 weeks (defined as 3 out of 4 or 2 out of 3 cortices with imaging confirmed bone bridging), in proportion of the recruited, treated patients. Data and images will be reviewed by an adjudication committee at the end of the study.

2.3 Secondary Endpoints

Secondary efficacy endpoints include quantification of the callus formation in the following variables:
-Amount of radiological callus at 6 weeks, 12 weeks, and 24 weeks (assessed by the adjudication committee).
-Changes in serum levels of bone turnover markers (in a centralized laboratory) at 6, 12 and 24 weeks after treatment: the following markers will be evaluated by immunoenzymatic assays on serum samples on all recruited patients:

- bone-specific alkaline phosphatase (BAP),
- C-terminal propeptide of Type I procollagen (PICP),
- intact osteocalcin and its N-terminal fragment (Intact-OC, Midtact-OC),
- carboxyterminal cross-linked telopeptide of Type I collagen, cross-laps (sCTX),
- osteoprotegerin (OPG),
- insulin like growth factor II (IGF II)
- receptor activator of nuclear factor NF- B ligand (RANKL).

Secondary safety endpoints include
-Complication rate as percentage patients with local bone complications regarding the non-union treatment in the FU.
-Complication rate as percentage patients with local and general complications regarding potential effects of introducing the biomaterial with MSC in the FU of patients.
Particularly, local complications specifically investigated will be:

- heterotopic ossification
- bone resorption
- osteolysis
- infection

-Other local or general complication rate.

-Economical impact: cost analysis compared to the alternatives in the literature (focusing on bone autograft and on other orthobiologics, particularly BMPs recommended in diaphyseal non-unions of the tibia).

3 STUDY DESIGN

3.1 Type of study

Prospective, multicenter, non-comparative Phase II interventional Clinical Trial to evaluate efficacy and safety.

3.2 Type of research

Clinical research is planned in this study to assess efficacy in the bone healing in different countries and facilities under the same protocol and standardised techniques. Patients under treatment will be followed in the mid-term until bone healing. Descritptive statistics and cost analysis are planned. On a practical point of view, the study will be planned as a prospective meta-analysis, as defined by the Cochrane Collaboration (http://www.cochrane.org/docs/pma.htm): a trial will be initiated within each participating country and data will be pooled at the end. Such an approach will allow taking into account local specificities of legal issues. Efficacy and safety issues, as well as cost analysis, will be compared to the literature (particularly, about the use of autograft and BMPs)

3.3 Study design (flow-chart)

FLOW CHART FOR ORTHO1

Trial period	Screening	Pre-treatment		Treatment	Follow-up		
Visit	1	2	3	4	5	6	7
	Screening	Bone marrow harvesting	Day before implantation surgery	Implantation surgery	6 weeks after surgery	12 weeks after surgery	24 weeks after surgery
Days	-30-0	1	17-30	18-31	59-73	101-115	185-199
Patient information and consent	X						
Demographics/Med History *	X						
Physical exam	X				X	X	X
XR exam	X				X	X	X
CT exam	X					X	X
Concomitant therapy	X						
Inclusion/exclusion criteria **	X						
Serum level of bone turnover markers ***		X			X	X	X
Adverse event/complication		X		X	X	X	X
Bone marrow aspiration		X					
Surgery at fracture site				X			
Other required surgery (eventual assoc. biopsy)					X	X	X
Conclusion of patient participation							X

* Patients should be asked if they are smokers and their Body Mass Index should be acquired.

** Inclusion/exclusion criteria may be based on medical history, demographics, X-rays, performed prior to bone marrow obtention.

*** Serum level of bone turnover markers: bone-specific alkaline phosphatase (BAP), C-terminal propeptide of Type I procollagen (PICP), intact osteocalcin and its N-terminal fragment (Intact-OC, Midtact-OC), carboxyterminal cross-linked telopeptide of Type I collagen, □-cross-laps (sCTX), osteoprotegerin (OPG), receptor activator of nuclear factor NF-□B ligand (RANKL), insulin like growth factor II (IGF II). 3 vacutainer 7mL.

3.4 Projected study timetable

3.4.1 Total duration of the study

Duration of the recruitment: 1 year.
Duration of the follow-up and treatment for each patient: 6 months.
Total duration (enrolment + follow-up + analyses): 2 years.

3.4.2 Projected study timetable

- Start of recruitment: 12/2011
- End of recruitment: 12/2012
- End of FU: 06/2013
- Core lab and biological analyses: + 6 months
- Statistical analyses and results: 12/2013

4 SELECTION OF PATIENTS

4.1 Study population

Age 18 to 65, both sexes (non pregnant or lactating women)

4.2 Patient recruitment and drop-out criteria

4.2.1 Inclusion

The inclusion criteria are :

- Age 18 to 65, both sexes (non pregnant or lactating women)
- Traumatic isolated comminuted closed or open Gustilo I and II humerus, tibial or femur diaphyseal or metaphysodiaphyseal fracture status delayed union or non-union
- At least 3 months from acute fracture
- Able to provide informed consent, and signed informed consent.
- For some European countries (example France and Spain): patients (by themselves) should have medical health care coverage to be included in a research study.
- Able to understand and accept the study constraints

To further standardize the inclusion, patients to be included will be those that alternatively would have received bone autograft and/or BMPs, thus avoiding (excluding) segmental defect patients to be treated with large allografts.

4.2.2 Non Inclusion

The exclusion criteria are :

- Participation in another therapeutic trial in the previous 3 months
- Delayed union or non-union related to iatrogeny
- Segmental bone loss requiring specific therapy (bone transport, large structural allograft, megaprosthesis, etc)
- Vascular or neural injury
- Other fractures causing interference with weight bearing
- Infection (skin, soft-tissue or bone)
- Visceral injuries of diseases interfering with callus formation (craneoencephalic trauma, etc.)
- Medical history contraindicating bone-marrow aspiration
- Corticoid or immunosuppressive therapy more than one week in the three months prior to study inclusion
- Pregnancy or lactancy at the day of inclusion in study, or pregnancy risk during treatment
- History of prior or concurrent diagnosis of HIV-, Hepatitis-B- or Hepatitis-C-infection (confirmed by serology or PCR)
- Adult in the care of a guardian
- Impossibility to meet at the appointments for the follow up
- Insulin dependent diabetes
- Autoimmune inflammatory disease
- Current treatment by biphosphonate or stopped in the three months prior to study inclusion.

4.2.3 Recruitment method

Patients treated in the participating Hospitals or its influence area, are eligible and will be offered the participation in this surgical trial as an alternative to bone graft, providing they accept, if required, complementary surgical techniques (osteosynthesis, intramedullary nailing, local debridement and/or others) and follow-up.
To further homogenize the recruited patient, the imaging and clinical data of the elegible patient will be forwarded to the other clinical centres participating in the study. The patient will be included if no centre is against this inclusion and at least one centre agrees on the inclusion.

4.2.4 Premature drop-out criteria

- Exclusion related to the decision of the subject enrolled (the subject is not obliged to specify the reason, this will be mentioned in the informed consent).

- Exclusion related to the treatment (at the appreciation of the investigator):

- Exclusion related to the progression of the disease or surgical complications: in case of implant failure, significant osteolysis, peri-implant fracture, infection.

4.2.5 Future of the dropped out patients

Exclusion related to the decision of the subject enrolled:

- The decision of the subject should be notified by a letter to the local investigator (and transmitted to the PI)
- The decision should not modify the quality of the management of the subject, and a regular medical follow-up will be recommended as for every relatives in such situation
- The treatment can be stopped immediately, without progressive decreased steps
- Results of prematurely dropped-out patients will be analysed in ITT but excluded in PP.
- In all cases, subjects who withdraw after informed consent, but before any therapeutic unit be used, will be replaced since the present study is not a randomized trial.

Exclusion related to the decision of the investigator, but unrelated to the treatment:

- The decision of the investigator, and the specific reason, should be notified by a fax and letter to the sponsor and the principal investigator.
- If necessary (example: pregnancy), the treatment can be stopped immediately, without progressive decreased steps.
- Results of prematurely dropped-out patients will be analysed in ITT but excluded in PP.

Exclusion related to the decision of the investigator, and related to the treatment:

- See chapter 8 (serious adverse effect).

4.3 Future of the patients after the end of the study

- The treatment under study is a single procedure, followed up during 6 months.
- If healing has not occurred, the patient may require additional treatment, under the care of the Hospital, the treating physician or Service, or the provider in charge of his process, even if unrelated to the study.
- When the results of the study analyses will be known, they will be diffused to the network of the investigators in order to help them to clarify the choice regarding the continuation or not of other treatments.
- Whatever the results, a medical follow-up of the subjects will be recommended, as for a subject in this situation.
- In case of failure or complication requiring a subsequent operation, bone biopsies will be performed to further verify the safety of the provided treatment.

5 EVALUATION CRITERIA

5.1 Primary evaluation criterion

Number of patients with proven bone healing at 6 weeks, 12 weeks, and 24 weeks (defined as 3 out of 4 or 2 out of 3 cortices with imaging confirmed bone bridging), in proportion of the recruited, treated patients.

5.2 Secondary evaluation criteria

- Secondary end-point 1:
    - Amount of radiological callus at 6 weeks, 12 weeks, and 24 weeks.
    - Changes in serum levels of bone turnover markers at 6, 12 and 24 weeks after treatment.

- Secondary end-point 2:
    - Local and general complication rate in the follow-up.
    - Economical impact.

6 SCHEDULE OF ASSESSMENTS AND STUDY PROCEDURES

See Table for summary in section 3.3 (Flow chart)

6.1 SCREENING OR INCLUSION VISIT (VISIT 0)

- This will occur in days -30 to 0 (not more than 30 days before starting of the participation in the trial and bone marrow harvesting). This would take place not earlier than 3 months after the acute fracture, and will include:
    - Patient information and consent:
        - inform the subject about the study and the possible enrolment, give them the information and consent form and give them time to read it

        - signature of the informed consent
    - Demographics
    - Medical History: anamnesis with medical interview, and physical exam (including data on smoking, weight and height to obtain Body Mass Index).
    - Concomitant therapy during the last month
    - XR exam
    - CT exam
    - Selection of patient according to the Inclusion/exclusion criteria
- The procedure to be followed in case of adverse events will be explained to the subject
- Scheduling of V1 (1-30 days later than V0, including bone marrow aspiration under sterile conditions), and of V2 and V3 (days 17 to 31 post bone marrow aspiration). Details are indicated in the "Information notice" that was delivered to the subject (clinical investigator: direct phone number should be provided).

6.2 VISIT 1 (1-30 days after V0)

- Bone marrow harvesting
- Planning of operative treatment
- Signature of informed consent of the planned operation (what kind of osteosynthesis, steps of operation, risks, chances,…

6.3 VISIT 2 (17-30 days after V1)

- Clinical examination
- Premedication by anaestesiology
- Preparation of the patient for surgery the next day.
- Blood sampling for possible needed blood transfusion
- Other case –dependent investigations needed before opération (ECG, Radiograph of the thorax,…)

6.4 VISIT 3 (1 day after V2)

- Operation on fracture site
- Postoperative Visit to the patient to look for complications (compartment syndrome, neurologic symptoms

6.5 VISIT 4 (6 weeks after V3)

- Clinical examination (swelling, signs of infection, scars, function, load bearing, pain (visual analog scale) blood flow, sensoric)
- Conventional radiographs
- Full weight-bearing capability (monopodal) and pain scale (0 to 10) in monopodal full weight bearing.

6.6 VISIT 5 (12 weeks after V3)

- Clinical examination (swelling, signs of infection, scars, function, load bearing, pain (visual analog scale), blood flow, sensory)
- Conventional radiographs
- CT-scan

- Full weight-bearing capability (monopodal) and pain scale (0 to 10) in monopodal full weight bearing.

6.7 VISIT 6 (24 weeks after V3)

- clinical examination (swelling, signs of infection, scars, function, load bearing, pain (visual analog scale) blood flow, sensoric)
- Conventional radiographs
- CT-scan
- Full weight-bearing capability (monopodal) and pain scale (0 to 10) in monopodal full weight bearing

6.8 Premature discontinuation of the study or premature close-out of site

Exclusion (of a subject) related to the decision of the subject enrolled:

- See chapter 4.2.5 “Future of the dropped out patients”

Exclusion (of a subject) related to the decision of the investigator, but unrelated to the treatment:

- See chapter 4.2.5 “Future of the dropped out patients”

Exclusion (of a subject) related to the decision of the investigator, and related to the treatment:

- See chapter 8 (serious adverse effect).

Premature close-out of site decided by the sponsor in the following cases:

- if the Investigator has received from the Sponsor, through the REBORNE Consortium, the Investigation Product, means and information necessary to perform the Clinical Study and has not included any subject after a reasonable period of time mutually agreed upon,
- in the event of breach by the Investigator of a fundamental obligation under this agreement, including but not limited to breach of the Clinical Study Protocol, breach of the applicable laws and regulations or breach of the ICH guidelines on Good Clinical Practice,
- if the total number of subjects are included earlier than expected.

In any case, through the REBORNE Consortium, the Sponsor will notify the investigator of its decision by written notice.

Premature close-out of site decided by the local investigator:

- The Investigator must notify (30 days prior notice) the Sponsor, through the REBORNE Consortium, of his/her decision and give the reason in writing.

In all cases (decided by the Sponsor, through the REBORNE Consortium, or by the Investigator), the appropriate Ethics Committee(s) and Competent Authorities should be informed according to applicable regulatory requirements.

Premature close-out of site decided by the Ethics Committee(s) and Competent Authorities:

Significant side effects (in terms of severity and / or frequency) must be reported to

the sponsor. In cases of serious adverse events (SAE), such as death, may be related to research and treatment administered, the SAE statement is sent to the sponsor (see conditions below, chapter 8.4) who in turn informs the monitoring committee (DSMB) and competent authorities. These authorities can decide to stop temporarily the conduct of the study, the time to research the causes of these AEs and see if there is a correlation between the treatment and the AE. The decision to suspend temporarily or permanently the study is notified by written notice to the sponsor that will notify all clinical sites by e-mails and written notice.

7 TREATMENT

7.1 Study treatments

7.1.1 Description of treatment administration

The principles and process of intervention are the same as for a contribution of spongy autograft, except that the fragments are replaced by biomaterial and cells. The procedure is performed under anesthesia and includes 2 stages:

1/ Preparation of the non-union site to receive the graft

The surgical approach will be, wherever possible:

- For the humerus: lateral approach between the muscles triceps and brachialis anterior to the lateral intermuscular septum.
- For the femur, preferably externally usually passing in front of the lateral intermuscular septum.
- For the tibia, the postero-medial or anterolateral approach.

Of course the first track will be geared to the incisions made previously.

The preparation of the site of graft will be the same as for bone autograft:

- Ablation of necrotic free bone fragments.
- Excision of fibrous tissue at least, to allow better mobilization of fragments in case of correcting a deviation, but it is not necessary in principle to remove any fibrous tissue as this may cause more devascularization.
- Decortication musculoskeletal which will create a vascularized bed on which the composite will be filed. It must be extended over the entire height of the grafted area and adjacent to the shaft above and below the area of nonunion on a minimum height of 2 cm. In the horizontal plane, decortication should be as wide as possible.

The stable fixation of the fracture is always associated. With a simple plaster in case of nonunion very tight, which is rare. In most cases, using a means of osteosynthesis including:

- by bone plate with screws, locked or not depending on the stability of the home
- by static or locked nail
- the external fixator or Ilizarov apparatus, when other means are not usable. These fasteners may be left in place after the establishment of the composite material.

This choice is often guided by the equipment used during the first intervention, which can also be preserved if it fulfills its role.

For the tibial diaphysis a complementary procedure can be performed on the fibula. If the fibula is solid, an osteotomy of the fibula may be associated, if a compression in the fracture is necessary, or if its deformation is opposed to the reduction of tibial deformation.

2/ The application of the composite (biomaterial + cells)

The mixture is placed on the previously prepared area to be grafted. The mixture biomaterial - cell has a pasty consistency that allows it to be affixed to the full extent of the prepared area as it will be done with spongy bone.

The operator will note the following parameters:

- the surface area (height and width) on which the mixture, to get an idea of

the surface on which the mixture was spread
• the volume of the used composite (biomaterial + cell)

The closure of the incision will be sutured in the usual manner with the different plans (fascial, subcutaneous and skin). If Redon drains are used to drain a hematoma possible, they should, if possible, be unaspirated to reduce the risk of sucking in the drain part of the cells used.

The postoperative (external immobilization by cast or splint, resting on the operated limb, rehabilitation of the adjacent joints, etc..) will be the same as if an autograft had been done.
The sponsor and the principal investigator will be informed about all new inclusions by a mail and a fax.

7.1.2 Presentation of the investigational product (IP)

The IP, as described in the Investigagor Brochure, is composed by a CE marked material (granulated biphasic calcium phosphate by Biomatlante) plus pluripotent MSCs from autologous bone marrow isolation, expanded under GMP protocol in associated facilities.

7.1.3 Description of the treatment units

One single administration of the IP is planned, in the context of surgical treatment of delayed union/non union of a diaphyseal or metaphysodiaphyseal fracture. Two 5cc syringes of the biphasic calcium phosphate preparation and the corresponding GMP expanded MSCs will be introduced at the end of the appropriate debridement and fixation.

7.1.4 Posologies

The dosage of this single administration will then be 10 cc of biomaterial, with $2x10^6$ cells per cc ($200x10^6$ bone marrow expanded MSCs).

7.2 Concomitant treatments

The following concomitant treatments are not authorized:
-Corticosteroid
-Biphosphonate
-Immunosuppresive associated treatment

All other concomitant treatments should be notified into the case report form (CRF: name, posology, start and end dates, indication).

7.3 Study Logistic

7.3.1 Study medication logistics

After enrolment, the clinical investigator will plan the surgical intervention to first obtain BM as per SOP, and secondly implant the IP when the cell is provided from the associated GMP facility.

The labelling of packages complies with the regulatory requirements of each country involved in the study, as well as the recommendations of the “European Guide to Good Manufacturing Practice”.
The label on autologous therapeutic units will bear the following information to avoid the risk of mismatching:
- Name of the study: “ORTHO1”,
- Protocol number, identification code of the therapeutic unit, patient’s identification number (inclusion number + surname and name + date of birth),
- Packaging, storage conditions, expiry date of the product and batch number
- Regulatory sentences: “Only use for biomedical research; Keep out of reach of children”, and country-specific regulatory sentences.
- Name and contact information of the sponsor name, the coordinator and the local principal investigator

The label will be verified by the local investigator double-checking the correlation of the patient’s identification number and the full name of the patient and date of birth, in order to guarantee that the autologous product arrives to the corresponding patient.

-Part to be filled by local investigator :
- local principal investigator’s name (filled by the centre) and centre number
- patient’s identification number (inclusion number + initials of surname and name),
-visit number

A detachable part, which should be affixed to the case report form will contain the protocol number, the therapeutic unit identification number.

The Labels on syringes will bear the following information:
- Name of the sponsor and coordinator
- Name of the principal investigator or centre number
- Study number
- Batch number
- Expiry date

The sponsor, coordinator, and the principal investigator will be informed about all new inclusions by a mail and/or a fax addressed by the local investigator within the next 24 hours of enrolment.

7.3.2 Biological samples logistic

Serum sampling will be performed at V1, V4, V5, and V6 for immunoenzymatic assays to evaluate changes in serum levels of bone turnover markers, such as bone-specific alkaline phosphatase (BAP), C-terminal propeptide of Type I procollagen (PICP), intact osteocalcin and its N-terminal fragment (Intact-OC, Midtact-OC), carboxyterminal cross-linked telopeptide of Type I collagen, cross-laps (sCTX),

osteoprotegerin (OPG), receptor activator of nuclear factor NF-kB ligand (RANKL), insulin like growth factor II (IGF II).

7.3.3 Statistical analysis

The responsible for the statistical analysis is Dr. Bruno Girardeau.
This team is independent from the principal investigator.
See section 10 for the details.

7.4 Biological sample collection in humans

7.4.1 Bone turnover markers in serum

Tissues or biological samples:

- Blood sampling (3 serum tubes of 7 ml each) will be performed at V1, V4, V5 and V6. Blood must be collected on an empty stomach in the morning between 7-9 am;
- Dosages will be performed at a core lab (IOR, Laboratorio di Fisiopatologia Ortopedica e Medicina Rigenerativa. Responsible for the project: Prof. Nicola Baldini).

Samples preparation:
The sample can be stored up to 8 hours between 2 and 8°C. The sample must be centrifuged within 2 hours of collection (or within 8 hours if stored at 2-8°C). Before centrifugation, reverse the tube gently 4 to 5 times. Centrifuge the specimens at 3000 x rpm for 15 minutes.

The serum is to be transferred into the 12 appropriate cryotubes (0.5 ml of serum per cryotube) provided by the Core Lab. The cryotubes are to be gently shaken in order to mix the serum before being frozen.

Samples labelling :
Each tube and cryotube will be tagged with labels containing the following information:

♣ Visit : (V1, V4, V5, V6)
♣Investigation Center number
♣ Patient identification number
♣ Patient Initials
♣ Date of blood collection

Information to be added on reference sheet:
♣ ORTHO1 study, Inserm
♣ Date and time of blood collection

Samples storage:
The cryotubes with serum must be frozen within 4 hours of collection. It is preferable that the specimens will be frozen at -70 degrees Celsius (-70° C), however if this is not possible at each investigator site, the serum may be frozen and stored at -20 degrees Celsius (-20° C).

High standard for quality control will be used locally and then in the core lab.

Six aliquot serum samples are to be sent in dry ice to IOR and 6 aliquots must be conserved at the investigation centre until the end of the study. This will be used only if the core lab encounters some problems with the analysis of the first aliquot of plasma. At the end of the study and after results of the analyses, the remaining aliquots will be destroyed.

Some information such as patient ID number, date of inclusion, date and time of blood collection, date of sending the first aliquot will be recorded in the CRF of the ORTHO1 study.

Management of samples after storage:
Each local investigator centre will send to the core lab one of the 2 aliquots of all enrolled patients at three moments: at the end of the enrolment period, then after M18 and M36.
The second aliquot must be conserved in the investigation centre until the end of the study.
A specific transporter will be used to transport the samples to the core lab in Bologna in dry ice according to Good Practices for biological samples (UN3373). The sample must arrive to the core lab within 24 hours (arriving date before Friday).
The local investigator should inform the investigator coordinator of each patient enrolment by mail and fax. When he will sent the samples, he must notify the coordinator and the core lab responsible (Dr Nicola Baldini) by fax and/or mail.

The assays will be performed by the core lab as follows: the 4 samples from a given participant will be analyzed to assay the evolution over time of the concentration of biomarkers.
If the core lab cannot analyse a sample, it will ask the concerned investigator centre to send the second aliquot backup.

7.4.2 Bone biopsies

In case of failure, bone biopsies will be performed as a safety verification. Standard management of the samples in the Pathology Department of each Hospital will be conducted. Sections will be made available to the Consortium for further investigation if required.

8 VIGILANCE OF THE TRIAL

8.1 Definition

Adverse event: An adverse event is considered to be, and must be reported as such, any harmful event appearing in a person who is participating in biomedical research, whether or not this event is linked to the research or to the Drug under experimentation that is addressed by this research.

Adverse Reaction: An adverse reaction is considered to be any adverse event appearing in a person who is participating in biomedical research, and that has been deemed by the investigator as likely **to be linked to the use** of the IP under experimentation regardless of the dose administered.

Unexpected adverse reaction: any adverse effect of which the nature, severity or change does not agree with the reference document.

New Fact: safety data which could significantly modify the evaluation of the risk-benefit ratio for the Experimental Drug or the trial.

Imputability: Individual analysis for a given notification of an existing link between the use of a health product and the appearance of an adverse effect.

Serious adverse event (SAE) or serious adverse reaction (SAR): any adverse event or adverse reaction that:
- results in death,
- endangers the life of the person participating in research,
- requires hospitalization or extends hospitalization,
- causes major or long-lasting handicap or disability,
- results in a congenital malformation or anomaly, and involving the drug regardless of the dose administered.

The expression "endanger life" is reserved for an immediate vital threat, at the time of the adverse event and this, independent of the consequences that palliative or corrective therapy would have.

Suspected unexpected serious adverse reaction (SUSAR):

Serious adverse drug reaction (SAR) that is unexpected or for which the development is uncommon (unexpected issue) observed during a clinical trial and for which there is a relationship with the experimental drug, whatever the tested drug or its comparator.

Medically Important events: Medically Important Events refers to certain clinical or biological events that do not meet the severity criteria above, but which can suggest toxicity, warrant special monitoring of the subjects exposed, put the subject in danger or require intervention in order to prevent one or other of the consequences mentioned for the serious adverse events according to the judgment of the sponsor or investigator.

Certain circumstances that require hospitalization are not concerned with the severity criterion: "hospitalization/extended hospitalization" such as:
- admission for social or administrative reasons

- hospitalization that is predefined by the protocol
- hospitalization for medical or surgical treatment that was scheduled before the research
- passage as an out-patient

Other cases of adverse events that do not meet the above definition of severity must also be **declared immediately:**
- events that require medical intervention in order to prevent progression to one of the aforementioned conditions
- potentially serious events or an event that is medically pertinent according to the judgment of the investigator.

The following will be treated as serious: Pregnancies that began or were detected during the trial.

Identification of the reference document used to define the unexpected nature of an SAE:
- Summary of product characteristics (SPC).

8.2 Responsibilities of the investigator

Safety reporting:
The investigator must inform the sponsor, without delay, starting on the day that he becomes aware, of all serious adverse events that appeared in the trial except those that are listed in the protocol or in the brochure for the investigator as not requiring any immediate notification. This initial notification is materialized in a written report and must be followed quickly by one or more additional detailed written reports.

Any SAE should be reported to the sponsor within 24 hours from the time when the investigator became aware of the event. SAEs should be followed up and follow-up reports should be sent to the sponsor until the resolution of the event.
Any SUSAR must be reported to the sponsor within 24 hours from the time when the investigator became aware of the event. SUSARs should be followed up and follow-up reports should be sent to the sponsor until the resolution of the event.

The investigator must document the event as best possible and provide, if possible, **the medical diagnosis** for it.

Each adverse event must be evaluated by the investigator which includes evaluating the severity and the causal relation between the adverse event and the INVESTIGATIONAL PRODUCT or the associated treatment(s) and/or with the research procedures.

The investigator must ensure that the sponsor, directly or through the REBORNE Consortium, receives the pertinent information for follow-up within 8 days following the first declaration.

8.3 Responsibilities of the sponsor:

Jointly with the investigator, the sponsor, directly or through the REBORNE Consortium, evaluates the causal relation between the serious adverse event and the Investigational Product, and the associated treatment(s) and the research.
He evaluates whether the adverse reaction is expected or unexpected by using the current reference document (appendix).

Within the regulatory timeframe, he declares all of the suspected unexpected and serious adverse reactions (**SUSAR**) to Eudravigilance (European Union Pharmacovigilance database), to the competent authorities and to the Ethics Committees and informs the investigators.

The regulatory declaration is filed within a maximum period of:
- 7 calendar days for unexpected serious adverse reactions that are fatal or that are life-threatening. In these cases, additional pertinent information must be sought and sent within another period of 8 days.
- 15 calendar days for all other unexpected serious reactions. Likewise, additional pertinent information must be sought and sent within another period of 8 days.
In the case of a blind trial, as a general rule, the sponsor declares the unexpected and serious adverse reactions to the health authorities and to the Ethic Committees after having lifted the blind nature on the Investigational Product.

He declares to Competent Authorities and to the Ethic Committees the new safety risks and sends them an annual safety report.

8.4 Evaluation of the intensity of adverse events

The investigator is asked to evaluate the intensity* of the adverse events observed in the person participating in the research and to note this in the CRF, either by using a scale for grading the adverse events provided in the annex to the protocol *(e.g. NCI-CTC classification for cancerology trials*), or by using more general terms such as:

Mild	does not interfere with normal daily activity
Moderate	partial limitation of normal daily activity
Severe	limitation of normal daily activity

*: The criterion of intensity must not be confused with the criterion of severity which is used as a guide in defining the declarative obligations.

8.5 Evaluation of causality

The investigator must evaluate the causal relation of the adverse events with the Experimental Drug, the comparator(s), any associated treatment(s) and the research. All of the adverse events for which the investigator or the sponsor deems that a causal relation can be reasonably suggested are considered as suspicions of adverse reactions.

8.6 Methods and declaration timeframe for the investigator in declaring serious adverse events

In order to comply with current regulations concerning the declaration of serious adverse events to the competent authorities, the investigator agrees to document the event, comply with the notification timeframe, and provide all of the information needed to analyze this event.

8.6.1 Declaration method:

Any serious adverse event (SAE) must be declared by the investigator regardless of its causal relation with the trial treatment(s) or the research as soon as he becomes aware of it, **within a maximum period of 24 calendar hours** via e-mail and fax to:

Institut Thématique Santé Publique - Recherche Clinique et Thérapeutique (ITSP – RCT)
Mission Réglementation et Qualité et recherche clinique (RQRC)
Fax: 01 44 23 67 10
Email: rqrc.siege@inserm.fr

AND

To to the WP5, the Coordinator, and the CRO
To the attention of: Prof. E. Gómez Barrena
Fax: +34.914269774
Email: enrique.gomezbarrena@uam.es

The investigator fills out the form for the initial declaration of a serious adverse event, located in the appendix of the CRF and dates and signs it.

For each event, he includes on the declaration sheets:

- A clear and detailed description of the event, **in the form of a diagnosis if possible,**
- The severity,
- The start and end date of the event,
- Whether or not the treatment of the trial was interrupted,
- How it has changed,
- The causal relation between this event and the product(s) in the trial, the pathology treated, another pathology, another treatment or a constraint linked to the research (period without treatment, additional examinations requested within the framework of the research, etc.),

The investigator must also attach a serious adverse event report, whenever possible:

- A copy of the hospitalization or hospitalization extension report
- Where applicable, a copy of the autopsy report
- A copy of all of the results of the additional examinations carried out, including the pertinent negative results by enclosing the normal values of the laboratory.
- Any other document that he feels is useful and pertinent

All of these documents will be made anonymous and will include the patient's identification no.

8.6.2 Monitoring patients in the case of the appearance of a serious adverse event

After it has been initially declared, the SAE must be followed up until it is resolved, i.e. until a level of stabilization is reached that is deemed acceptable by the investigator or a return to the prior condition, even if the patient has left the trial.

The investigator has to

- collect any additional information concerning the SAE as soon as he becomes aware of it and note it on the form for the additional declaration of a serious adverse event,
- fax it as well as the results from laboratories or the hospitalization reports within **a maximum of 24 hours according to the same methods as the initial declaration**

8.6.3 Declaration period

All SAEs must be declared, if occurring for a patient:

- starting from the date the consent agreement was signed,
- throughout the entire period for monitoring the participant scheduled by the trial,
- up to 30 days after the end of the monitoring period provided for by the trial, when it is caused by the research,
- with no limitation to the duration when it is likely to be due to the Investigational Product (this involves for example serious effects that can appear a long time after exposure to the drug, such as cancers or congenital anomalies).

8.6.4 Annual safety report (ASR):

On the anniversary date of the first trial authorization delivered by a Competent Authorities, the sponsor drafts, in collaboration with the Investigator Coordinator, a safety report including:

- The list of the serious adverse events likely to be linked to the Experimental Drug undergoing experimentation in the trial including the expected and unexpected SARs.
- A concise and critical analysis of the safety of the patients that are participating in the research.

This report can be submitted to the coordinating investigator for approval.
This report is sent to the Competent Authorities and Ethic Committees within the 60 days following the anniversary date of the 1st authorization of the trial.

8.7 Other events to notify

8.7.1 Declaration methods in the case of in utero exposure

If a woman falls pregnant during the research, the investigator in charge of monitoring the patient must provide information by fax and e-mail when he becomes aware of it **within a maximum of 24 calendar hours**:

Institut Thématique Santé Publique - Recherche Clinique et Thérapeutique (ITSP – RCT)
Mission Réglementation et Qualité et recherche clinique (RQRC)
Fax: 01 44 23 67 10
Email: rqrc.siege@inserm.fr

AND

To to the WP5, the Coordinator, and the CRO
To the attention of: Prof. E. Gómez Barrena
Fax: +34.914269774
Email: enrique.gomezbarrena@uam.es

The investigator notifies the pregnancy using the initial data collection form for the pregnancy, located in the appendix of the CRF. This form must include the contact information of the obstetrician and of the maternity ward where the birth is scheduled.
The investigator must monitor the patient until the term of the pregnancy or until it is interrupted and inform the sponsor of the results using the final data collection form for the pregnancy, located in the appendix of the CRF.
The form is filled out in collaboration with the obstetrician and sent by fax following the same methods as the initial declaration.

Warning:
Any voluntary pregnancy termination (VPT), therapeutic interruption of pregnancy (TIP) or miscarriage must be filed as a pregnancy declaration.
If the end of the pregnancy falls within the framework of the definition of the serious adverse events (spontaneous abortion with hospitalization, death of the fetus, congenital anomaly, etc.) the investigator must follow the procedure for declaring SAEs.

8.8 Conduct in the event of a non-serious event

All non-serious adverse events and/or abnormal analysis results, defined in the protocol as being determinant in evaluating the safety of the people who are participating in the clinical trial shall be reported on the CRF, they will be followed until resolved. The investigator will judge the causality of the Investigational Product of the trial and pathology.
The degree of severity of a biological adverse event shall be assessed over 2 samplings taken as close together as possible.

8.9 Conduct in the event of an adverse event

All adverse events independent of their classification should be reported to the principal investigator. If a relationship between the event and the study treatment is proposed, a biopsy shall be taken and analyzed.
After evaluation of the cause the investigator will report the event to the Ethics Comittee and further steps will be planned. E.g. exclusion from the study, surgical debridement of the fracture site and the cell-scaffold contruct, or other.

8.10 New Risks

In the event a new risk appears that is inherent to the research and likely to affect the safety of the patients who are participating in it, the sponsor and the investigator will take suitable emergency safety measures.

The patients must be informed about the new risk occurred.

The sponsor will immediately inform Competent Authorities and Ethic Committees concerned by these new risks and, where applicable, the measures taken.

8.11 Independent monitoring committee

An independent Data Safety Monitoring Board (DSMB) will meet at least once a year to check how the study is conducted. This DSMB will be formed by the members of the Ethical Advisory Board (EAB) of the REBORNE project and the members of the Scientific Advisory Committee (SAC). The purpose of this board is to assess the safety data and conclude whether it is safe to continue the study. Data to be analyzed include safety reports, and the based on these, the DSMB will provide annual but also urgent reports, including the possibility to decide the end of the study.

8.12 Scientific board

The scientific board is composed of the EC of the Consortium REBORNE that includes representatives of the sponsor (in the Coordination of the project).
It is involved in the decision-making process and plays a part in every aspect of the study, including amendments.

9 DATA COLLLECTION AND PROCESSING

9.1 Description of collected data

Data collected are indicated in the CRF in Appendix.

9.2 Data collection

The CRF will be completed for each patient included in the study, after verification versus source data by the clinical monitor in each centre.

Prior to archiving, each CRF will be dated and signed by the investigator and then stored in the investigator file. Archiving of the CRFs and investigator files will be done by the trial centres according to GCP, under the responsibility of each Principal Investigator.

Data collection will be performed, in accordance with Good Practices, under the responsibility of the local investigator.

The original pages of the CRF will be collected by the monitor after source data verification and sent to data management.

9.3 Data processing, checking and authentication (data – management)

During the study, the local investigator will authorize the monitor to visit the site and facilities used for the study; to check all the CRF paper copy to make sure they are filled in correctly, to compare them with the original data (patient medical file). The follow-up study will be carried out at regular intervals, which will be agreed by the investigator and the monitor.

Double data entry will be performed to introduce the data into the study database.

The data manager will make plausibility checks and issue query notes to the sites for clarification of the discrepancies. The resolved queries will be verified versus source data by the monitor.

After cleaning of the database, it will be locked and data will be ready for analysis.

9.4 Storage conditions and management of study related documents

The investigator should keep, as long as possible and not less than 15 years after the study has ended, the following study related documents:

- Hard copy of CRFs,
- patients' source documents (originals)
- patients' identification codes
- signed informed consent forms (these documents are strictly confidential and, as per GCP, stored only at the investigational site)

- investigator file

All study related documents should be kept by the sponsor for at least 15 years after the completion of the Trial.

10 STATISTICAL ANALYSIS

10.1 Responsible for statistical analysis

The INSERM CIC 0202, Tours Hôpital, France, will have full access to data and take full responsibility for the integrity of the statistical analyses.

This team is independent from the principal investigator, and is independent from the biomaterials company and the biological biomarkers company.

10.2 Sample calculation

This is a phase II therapeutic, multicentre, non comparative, European trial.

In absence of any data, the number of cases to be included was not calculated but fixed at 30.

With such a sample size, the proportion of patients with proven bone healing will be estimated with a precision varying between 0.09 (95% confidence interval width) in the best case of a proportion of 0 or 1, and 0.374 in the worst case of a proportion of 0.5.

10.3 Description of the statistical analysis plan (choice of comparisons and methods)

This study has been defined according to the specific rules for clinical trials in orphan diseases (EMEA Guidelines on clinical trials in small populations, CHMP/EWP/83561/2005), http://www.emea.europa.eu/pdfs/human/ewp/8356105en.pdf

10.3.1 Analysis of criteria

Analysis of principal criterion

The radiologic analysis will be done in a first step by the treating Hospital (treating surgeon and/or radiologist). A diagnosis of bone consolidation/non consolidation will be issued at X-ray and/or CT in the FU visits.
The final radiological adjudication will be performed by a Committee formed by 3 senior specialists (Trauma surgeons and Radiologists), blinded to the Hospital treating the case. Consensus upon adjudication will be sought upon digital images.
On a statistical point of view, the data analysis will be descriptive. Proportions of patients with proven bone healing will be point estimated and by means of exact 95% confidence intervals.

Analysis of secondary criteria

Amount of radiological callus will be analyzed in the framework of a mixed model (thus taking into account correlation between repeated assessment of the same subjects), considering time as a categorical variable (thus preventing from the

hypothesis of a linear evolution). Such a model will allow the assessment of association between baseline characteristics and response to treatment, as assessed through radiological callus.

Complication rate will be assessed by point estimates and associated exact 95%CI..

Economical impact: Cost analysis of the investigated treatment will be provided. The treatment duration until radiological healing will be compared to the healing time of the conventional treatment (autograft and/or BMPs) according to the literature. The economic value of one average labour day and the economic costs of both treatments will be counted. Then the economic impact (treatment time in respect of the treatment costs) of both treatments will be defined for each participating country.

10.4 Population to be analyzed

The efficacy analyses will be performed according to both the intention-to-treat principle (all patients who received the investigational product in a surgical procedure), and the per protocol principle (thus excluding patients who had non allowed co-medications for instance).

A “blind” review will be conducted prior freezing the data base

The safety analysis set will include all patients who received study medication.

All tests will be two-sided. The level of significance for all analyses will be set at 0.05.

Software. Statistical analyses will be performed using SAS and R.

11 COMMUNICATIONS

The trial will be registered on Clinical Trial (clinicaltrials.gov) before the inclusion of the first participant. The trial will also be registered and announced on the web site of the Consortium (www.reborne.org) and the sponsor INSERM (France).

Procedures to undertake before publications or communications linked to the study are indicated in the consortium agreement (CA) already signed by Inserm and local structures involved, according to the general process of FP7 HEALTH F5-2009-241879 network.

Results from this study may be presented at scientific congresses or published in medical journals. Publications projects and conclusions will be jointly discussed by the Trial coordinating investigator (Prof E. Gómez-Barrena, PI), the European project coordinator (Prof. P. Layrolle), the scientific board, the biostatistician and the sponsor (INSERM), as regards to their contents and conclusions before final versions of abstracts, texts and posters are disclosed. This restriction applies also to modifications that could be required subsequently by the review board of congresses and scientific journals. The coordinating investigators, the biostatistician and the sponsor agree also not to publish study results prior to obtaining written agreement from all other parties.

Potential conflict of interest of co-authors will be addressed in any publication reporting the results of the study.

The full intellectual property of the trial belongs to the REBORNE Consortium network.

Global results of the study will be indicated, after publication acceptance, on the web site of the REBORNE Consortium. These global results will be also directly addressed to the persons having participated to the trial, upon request (but individual data will remain blinded and not available).

Global results of the study, after publication acceptance, can be indicated to a participant to the trial, upon request to the local clinical investigator or to the principal investigator.

Access to data (for further scientific analyses) once the study will be completed and published will be discussed upon request (example for pooling data for future meta-analyses). The decision will be taken by the Scientific Board.

12 CONFIDENTIALITY

CRFs will identify patients by their centre number, inclusion number, the first letter of their last name + the first letter of their first name (except in Germany, where the use of initials is forbidden).

Persons working under the supervision of the sponsor or the coordinator are obliged to respect confidentiality.

Direct access to clinical data and source documents will be given to persons in charge of monitoring, sponsor funded audits and inspections performed by relevant regulatory authority.

The database used in the study was developed and is hosted in France and will be declared to the computer national regulation institution in France.

This study follows the “reference methodology” (MR-001, dispositions de l’article 54, alinea 5, loi du 6 janvier 1978, modifiée relative à l’informatique, aux fichiers et aux libertés). Inserm, sponsor of the study, has signed a conformity agreement to the methodology.

The study has to be approved by Data protection agencies of each country involved, in compliance with national regulations.

13 PROTECTION OF PERSONS

13.1 Expected benefits and risks

Expected benefits of the study are related to treatment that will most probably improve the health status of the participating patient. There will be no financial benefits for the patients.

The risks are expected to be very low; therefore the benefit/risk ratio is expected to be very high.

Treatment of delayed bone unions and non-unions have a risk of failure to obtain consolidation, but also risks related to repeated surgical intervention of the site (particularly, infection, secondary scars, atrophic scars, muscle fibrosis, muscle necrosis, bone necrosis, fibrotic union of the fracture, atrophic non-union, heterotopic ossification, osteolysis).

Treatment with biomaterial and MSCs also sustain this risk of failure to obtain consolidation, but also risks associated with implantation at a surgical site following one or various surgical procedures. Therefore, the mentioned risks are also present, and infection risks is increased with any biomaterial implantation due to the potential bacterial colonisation of an inert biomaterial, in comparison to living bone tissue. This infection risk will be carefully controlled, both locally and systemically, in patients receiving the IP treatment, and will be compared with the literature.

Other potential risks such as immunological reactions are not considered in this case, as MSCs are originally autologous. However, any suspected immunological reaction will be carefully investigated.

Other potential risks such as tumorigenesis are not considered in this case, as autologous expanded cells have been checked in vitro and in vivo for genetic stability, without any detectable change. However, imaging techniques to be applied in the follow-up of the patients would allow to detect any significant bone destruction or bone production in the sense of osteolytic or osteoblastic tumor formation. As a supplementary safety control, bone biopsies will be obtained from the non union site in case of treatment failure during a subsequent surgery.

13.2 Ethical and regulatory provisions

The study will be performed in compliance with all applicable ethical and regulatory requirements in each participating country, the Declaration of Helsinki (appendix), the applicable EU directives (appendix), as well as Good Clinical Practices guidelines (appendix) and this protocol.

The investigators agree to perform the study in accordance to these ethical and regulatory requirements. They are aware of the fact that all study related documents and data may be audited or inspected in compliance with the patient's confidentiality and privacy and that any concerns about patient's rights cannot be used to refuse such audits or inspections. The investigators understand that the results of the study

are property of both the FP7/REBORNE network and the sponsor of the study (Inserm).

13.3 Ethics committee

Prior conduction of the study, the sponsor will submit the project to the relevant Ethics Committees and Regulatory Agencies. The following core documents will be submitted: study protocol, Case Report Form, Patient's information form, Informed Consent form, (appendix 3). In each centre, the submission file will be made according to the local requirements.

The study cannot be started on a site until the sponsor receives an unreserved favourable opinion of the Ethics Committees regarding the submitted protocol and all relevant documentation.

The sponsor will inform the Ethics Committees of all amendments and all serious or unexpected adverse events or any new event occurring during the study and which could likely affect the safety of the subjects included in the study.

In France, the protocol is submitted by Inserm to the CPP
In Italy, the protocol is submitted by IOR to the Ethical Committee of the Istituto Ortopedico Rizzoli and to the National Authority for Pharmaceutical Investigations (AIFA, Agenzia Italiana del Farmaco)
In Germany, the protocol is submitted by University of Ulm to the Local Ethics Committee (Ethics committee of the University of Ulm) and to Paul-Ehrlich-Institut as the regulatory authority.
In Spain, the protocol is submitted to La Paz Hospital Local Ethics Committee and to the AEMPS (Agencia Española del Medicamento).

13.4 Insurance and financing

The sponsor is responsible for taking out insurance in accordance with local regulatory requirements.
In accordance with European legal and regulatory requirements regarding biomedical research, the Inserm, has taken out, prior to study start, a liability insurance policy ("Responsabilité Civile"; Gerling France, 111 rue de Longchamp, 75116 Paris, n° XXX) for the entire duration of the study (appendix).

13.5 Information to patients and informed consent

In accordance with local applicable regulatory requirements, before any study specific procedure is performed, the investigator should obtain a signed informed consent from the subject included in the study.

The informed consent will be collected at inclusion.

The information will be given orally and in writing using the information form (appendix 3). The form should be initialled signed at the bottom of each page showing that the subject has received this information. The information form should

be written in a clear and fully understandable language term. It should contain all the information that should be given to the person. If necessary, local versions of informed consent will be created for the participating countries.

The consent to participate in the study is given by writing in the Consent Form (appendix 3). This should be written in a clear and fully understandable language for the person participating in the study. The subject included in the study gives his/her consent by writing the first and last name, the date and by signing the form. The informed consent form is signed and dated by both patient and investigator in 2 originals.

Furthermore, the investigator who collects the consent form should date and sign the appropriate part of the form and ensures that: 1) the form is correct and that no information is missing; 2) an original of this document is given to the patient; and 3) a second original should be kept in the investigator file.

The investigator should ensure that the subject included in the study has enough time to read and understand the Information and Consent Form and to make his/her decision freely.

Prior to the start of the study, the Information and Consent Form should first be approved by the relevant local Ethics Committee during the assessment process of the submission file.

14 QUALITY ASSURANCE

14.1 Investigator and sponsor obligations

The study will be performed in compliance with all applicable ethical and regulatory requirements in each participating country, the Declaration of Helsinki (appendix), as well as Good Clinical Practices guidelines (appendix) and with the relevant laws and regulations of the countries in which the research is performed.

14.2 Quality control

Monitoring will be funded by the European project REBORNE funds in France and in other European countries.

The coordinating centres (INSERM and Principal investigator team) will be in charge of the study coordination, insuring all study requirements within Europe: centres initiations, study follow-up, data management, supervision of the monitoring activities and reporting in accordance with the established standard operating procedures, the GCP and the regulatory affairs.

A subcontracted Clinical Research Organization will be in charge of the monitoring in the centres. Local monitors will be recruited by the sponsor or by local investigators to realize the monitoring in their own country, in accordance to the study procedures. The CRO has to inspect the case report forms, following the established procedures (number of visits, delay between visits…). Monitoring visits will be performed in each investigator sites, in order to check adherence to protocol and legal aspects and accuracy of data collection. The CRO shall access all patients' records: patient's files

or any other documents needed to check the CRF. The presence, likelihood and coherence of the data will be controlled in the database, following pre-established rules. Queries will be edited when corrections are detected and needed.

At least 3 monitoring visits will be realized per patient included in the study.

The investigator should allocate sufficient time to these visits and give the monitor access to source documents which prove accuracy of information written in the CRF: patient's medical record, laboratory results, appointment book.

The principal investigator and the co investigators agree to be available at each visit of monitoring. During these visits, the following aspects will be checked:
- informed consent,
- adherence to protocol and established standard operating procedures,
- quality of the collected data: accuracy, missing data, coherence with patients' records (medical file, visit agenda, laboratory results…)
- study drug management safety (AE, SAE, SUSAR)

Persons in charge of the quality control of a biomedical research are mandated by the sponsor. They have access, with the concerned persons' agreement, to individuals data strictly required for this control. These persons are obliged to respect professional secret. Each visit will be followed by a complete written report.

14.3 Audit and inspection

Regarding an audit or an inspection of the trial, the investigator agrees to adhere to the sponsor demands and to its health authority.
The audit could be performed at any time during the study, and 15 years after its ending.

15 PROTOCOL AMENDEMENTS AND MODIFICATIONS

Any substantial modification of the protocol should be submitted to both the scientific board and the sponsor. If approved, the amendment will have to be submitted to local competent authority and ethic committee of each country prior to its implementation.

16 APPENDICES

Appendix 1: REBORNE HEALTH F5-2009-241879 general project (FP7/UE)
Appendix 2: Summary of Products Characteristics
Appendix 3: Information and consent forms
Appendix 4: Case Report Form
Appendix 5: Investigation centres

Appendix 6: SAE forms
Appendix 7: Insurance
Appendix 8: CPP (French Ethic Committee) agreement
Appendix 9: AFSSAPS (French Competent Authority) authorization
Appendix 10: Declaration of Helsinki
Appendix 11: Good Clinical Practices
Appendix 12: The applicable EU directives

Attachment 2: Maxillo 1 protocol

ImBioCeSM Protocol

Eudract: No. **EC Ref.:**
Ref: BRD/

***ImBioCeSM**: Implant placement after filling with a Biomaterial and mesenchymal stem cell combination*

"Clinical trial: Jaw bone reconstruction using a combination of biomaterial and autologous mesenchymal stem cells prior to dental implant placement"

Coordinator :

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Sponsor:

CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

Nantes University Hospital
Clinical Research Promotion Department
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Technical Support Centers:

The MSCs will be prepared at the French Blood Institute (EFS)/ local equivalents in compliance with the agreement reached between the different partners

FOR NANTES

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FOR BERGEN

GMP facility iin Bergen will be available the summer 2011

FOR LIÈGE

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FOR VERONA

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Universitaria Verona, Policlinico G.B. Rossi, P.le L.A. Scuro 10, 37134

SUMMARY

The summary must not exceed three pages and must clearly and accurately present the principal characteristics of the protocol and its scientific relevance.

Study title	International, multicenter phase II uncontrolled prospective cell clinical trial: Jaw bone reconstruction using a combination of biomaterial and autologous mesenchymal stem cells prior to dental implant placement **ImBioCeSM**: Implant placement after filling with a Biomaterial and mesenchymal stem cell combination
Key words	Jaw bone reconstruction, biomaterial, autologous mesenchymal stem cells, dental implant placement
Study sponsor	**NANTES UNIVERSITY HOSPITAL**
Trial coordinator (in the case of a multicenter trial)	Pierre CORRE - Medical doctor – assistant professor Oral and Maxillofacial Surgery Nantes University Hospital*:* Hôtel-Dieu 1 place Alexis-Ricordeau 44093 Nantes Cedex 1, France Telephone: + 33 (0) 2 40 08 36 79 Fax: + 33 (0) 2 40 08 36 68 pierre.corre@chu-nantes.fr
Number of centers	International multicenter trial regrouping 4 clinical centers
Type of study	Cell therapy
Study schedule	❖ Total duration: 3 years ❖ Recruitment period: 12 months ❖ Treatment duration per patient: 12 months ❖ Duration of follow-up per patient: 24 months
Study design	❖ Multicenter ❖ Phase: 2 ❖ Uncontrolled ❖ Non-randomized ❖ Prospective
Study objectives	Principal objective: placement of dental implants in bone reconstructed with a combination of biomaterial and mesenchymal stem cells Secondary objective(s): morbidity associated with autologous bone marrow harvesting. Mid-term (24 months), assessment of implant stability at the site of the graft*.*
Number of cases scheduled	40 (10 cases per clinical center)
Schedule of the various visits and examinations	To be filled in when protocol will be validated

Principal selection, inclusion, non-inclusion and exclusion criteria	To be filled in when protocol will be validated
Treatment, medical device, cell therapy product, study procedure	To be filled in when protocol will be validated
Reference treatment (if applicable)	Not applicable
Principal assessment criterion	To be filled in when protocol will be validated
Secondary assessment criteria	To be filled in when protocol will be validated
In the event of ancillary studies: no ancillary study	
Other assessments	To be filled in when protocol will be validated
Statistical analysis	The following variables will be taken into account for the statistical analysis of the principal criterion: The height and width of the reconstructed ridge, the initial height of the ridge + height of the graft greater than or equal to the length of the prescribed implant (median of the values measured independently by the investigator during the pre-implant consultation, a dental surgeon and a maxillofacial surgeon, and centralized at the end of the study), the initial width of the ridge + the width of the graft greater than or equal to the length of the prescribed implant + 2 mm (median of the values measured independently by the investigator during the pre-implant consultation, a dental surgeon and a maxillofacial surgeon, and centralized at the end of the study), any contraindications viewed in the scan: sinusitis, osteitis. Signs of inflammation or local or general infection preventing the placement of the implant (excluding other general contraindications), clinical appraisal of the height of the reconstructed bony ridge using a VAS on palpation after incision of the mucosa before placement of the implant, ISQ values, assessment of pain and difficulty in walking (VAS, recording of the number of day(s) the patients experienced pain/difficulty in walking if the VAS >= 1), intensity of the pain, the period of professional inactivity (sick leave, leave without pay), functional limitations, healing times, the use of painkillers, complications related to the study procedure (particularly at the harvest sight and at the receiving site: clinical and radiological examinations), results of the qualitative/quantitative assessment of bone regret, The principal criterion will be assessed for the proportion of patients for whom implant placement is confirmed at ~~9~~6 months. The proportion of patients will be estimated selectively and with an accurate confidence interval. The other variables taken into account for the statistical analysis will be described in terms of frequency and percentage for qualitative variables and in terms of median, minimum and maximum values for quantitative variables. The analyses will test for a correlation with smoking .

	As this study is a descriptive study, the variables of all the patients will be taken into account on condition that the patient is treated with the hybrid bone graft combining calcium phosphate ceramic scaffold and mesenchymal stem cells

SIGNATURE PAGE

SIGNATURE OF THE SPONSOR

The sponsor undertakes to conduct the study according to all the legislative and regulatory provisions that apply to research and in compliance with the protocol.		
Name and function of the sponsor's representative:	**Date:**	**Signature:**

SIGNATURE OF THE INVESTIGATORS

I have read all the pages of the clinical trial protocol sponsored by the Nantes University Hospital. I confirm that the protocol contains all the necessary information required to conduct the trial. I undertake to conduct the study respecting the protocol and the terms and conditions defined therein. I undertake to conduct the study taking into account:

- The principles of the "Declaration of Helsinki",
- International Good Clinical Practice rules and recommendations (ICH-E6) and French rules (Good clinical practices for biomedical research on medicines for human use – decisions dated 24 November 2006)
- National legislation and regulations concerning clinical trials,
- The Clinical Trial Directives of the EU [2001/20/EC]

I also undertake to ensure that the investigators and other qualified members of my team will be provided access to copies of the protocol and documents concerning the study so that they can take into account the provisions contained therein.

Trial coordinator	**Name:** **Dr Pierre LAYROLLE** INSERM U791	**Date:**	**Signature:**
Principal investigator	**Name and institution:** **Dr Pierre CORRE** CHU de Nantes	**Date:**	**Signature:**
Methodologist:	**Name, function and contact details:** **Dr Bruno GIRAUDEAU** INSERM CIC 0202	**Date:**	**Signature:**
Cell Medical and Scientific Manager	**Name, function and contact details:** **Dr. Luc SENSEBE** **Medical and Scientific**	**Date:**	**Signature:**

	Director EFS Centre-Atlantique		

LIST OF ABREVIATIONS

Table to be completed based on the contents of the protocol

AFSSAPS	*Agence Française de Sécurité Sanitaire des Produits de Santé* French Health Products Safety Agency
MA	Marketing Authorization
CRA	Clinical Research Associate
GCPs	Good Clinical Practices
EC	Ethics Committee
CNIL	*Commission Nationale de l'Informatique et des Libertés* Independent French administrative authority whose mission is to ensure that data privacy law is applied to the collection, storage, and use of personal data
CRF	Case Report Form
MSCs	Mesenchymal Stem Cells
SAEv	Serious Adverse Event
SAE	Serious Adverse Effect
USAE	Unexpected Serious Adverse Effect
ICH	International Conference on Harmonization
INSERM	*Institut National de la Santé et de la Recherche Médicale* French National Health and Medical Research Institute
MBCP	Microporous biphasic calcium phosphate
RM	Reference Methodology
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
CTT	Clinical Trial Technician
CTP	Cell Therapy Product

CONTENTS

INTRODUCTION

Edentulism in the posterior region of the jaw may cause masticatory and articular disorders. Alveolar bone melting caused by tooth loss is often a contraindication for implant-borne prostheses. This solution, which is recognized as the most efficient, can only be envisaged after bone reconstruction.

Autologous bone grafting is considered to be the gold standard in reconstructive surgery but it is associated with a certain degree of morbidity. Bone substitutes, used as an alternative, are not very effective when reconstruction involves a significant amount of bone in a poorly vascularized environment.

Tissue engineering techniques combining autologous cells and biomaterials have resulted in to several phase I studies being conducted in Europe over the last few years, particularly in pre-implant surgery. The clinical results obtained in these studies did not equal those obtained with autologous bone grafts, but they provided evidence that it will be possible, in the near future, to achieve bone reconstruction as reliable as that obtained with the reference technique, but in a less invasive manner.

The purpose of the ImBioCeSM project is to reconstruct edentulous jaws for prosthetic rehabilitation using a combination of autologous mesemchymal stem cells (MSC) and a bone substitute consisting of synthetic microporous biphasic calcium phosphate (MBCP) and a minimally invasive, standardized and safe surgical procedure.

1. STUDY RATIONALE

1.1. THE SITUATION IN TERMS OF RESEARCH

1.1.1. Inventory

Edentulism in the posterior region of the jaw, irrespective of whether it is of degenerative, traumatic of infectious origin, may cause masticatory and articular disorders. With the lengthening of life expectancy in Europe, these symptoms are the source of increasingly frequent complaints made by the general population to health professional. Bone melting caused by tooth loss is often a contraindication for implant-borne prostheses, recognized as the most effective way to treat the problem. Use of such prostheses can only be envisaged after preliminary bone reconstruction of the edentulous jaw, and close to a third of implant candidates fall into this category of patients.

Despite the satisfactory results obtained with bone grafts, which is accepted as the reference method, potential morbidity is indisputably associated with the graft harvest site (Finkemeier 2002). Alternatively to bone grafts, bone substitutes of animal, human or synthetic origin may be used alone to reconstruct small defects (often smaller than a few milliliters), but they have been found to be less effective when large areas affected by loss of substance need to be repaired.

The search for alternative solutions has resulted in several teams developing tissue engineering procedures (Kuriakose, Shnayder et al. 2003) which combine bone substitutes and autologous mesenchymal stem cells.

Of the biomaterials used, synthetic calcium phosphate ceramics are particularly valuable for bone engineering. These ceramics are widely used to repair bone defects in orthopedic, spinal, maxillofacial or dental surgery (Veron, Chanavaz et al. 1995; Hornez, Chai et al. 2007). Synthetic bone substitutes, in addition to being innocuous in terms of pathogen transmission, demonstrate bioactivity and osteoconduction properties. These materials are most often made of hydroxylapatite (HA: Ca10(PO4)6(OH)2), tricalcium bis(phosphate) beta (β-TCP: Ca3(PO4)2) or consist of mixtures of the two phases (biphasic calcium phosphate, BCP) in variable proportions (Veron, Chanavaz et al. 1995; Hornez, Chai et al. 2007). The micro- and macro-porous properties of BCP permit invasion of biological fluids, cells and tissues. The concept of bioactivity is based on the different solubilities of the crystalline phases constituting the BCP. β-TCP, which is soluble in biological fluids, liberates calcium and phosphate ions that lead to the precipitation of apatite crystals on the less soluble HA phase. This layer of biological apatite serves as a substrate for osteoblasts that can adhere to the surface of the material and synthesize the extracellular matrix of the bone. This results in bone growing again on contact with the biomaterial, by osteoconduction. The resorption of BCP bioceramics is relatively slow and they are substituted by mature bone tissue over a period of 6 months to 2 years depending on the site of implantation and the physicochemical characteristics of the material.

In 1974, Friedenstein (Friedenstein, Deriglasova et al. 1974) showed that bone marrow (BM) contains osteogenic precursor cells, i.e. mesenchymal stem cells (MSC). These cells (1 / 100,000 nucleated cells in adults) were isolated thanks to their capacity to adhere to plastic. Mesenchymal stem cells have the ability to renew themselves and are multipotent, capable of developing into a variety of cell types depending on the culture medium in which they are cultured. Many studies have shown that if these cells are seeded and/or cultivated on calcium phosphate ceramic matrices, they can induce bone formation *in vivo*. Recent works have shown that BCP ceramics consisting of HA/β-TCP 20/80 are the best matrices for MSC culture *in vitro* and bone formation *in vivo* (Arinzeh, Tran et al. 2005). The bone marrow is not the only source of mesenchymal stem cells. The periosteum, fatty tissue or dental pulp are also interesting cell sources.

Bone tissue engineering combining mesenchymal stem cells with bioceramic matrices is an emerging field that has yet to be fully developed and most of the pre-implant surgical studies conducted have been preclinical or early clinical trials (phase I & II).

To our knowledge, only a few teams have been able to provide evidence of the clinical value of the concept.

1.- En 2002, IsoTis Orthobiologics (Bilthoven, Hollond) conducted 2 phase I clinical trials on the use of autologous osteogenic precursor cells combined with calcium phosphate matrices. One study, involving 10 patients concerned the increase in maxillary bone before insertion of dental implants with radiological and histological analyses (Meijer, de Bruijn et al. 2007). The second study also included 10 patients and investigated the reconstruction of the acetabulum during hip implant revision. In both clinical trials, osteogenic precursor cells were isolated from the bone marrow of the patients and amplified for 3 weeks in the clean rooms of the company. The cells were then cultured and differentiated on ceramic matrices before clinical use. The results obtained proved that the therapeutic approach is feasible and innocuous. However, the bone tissue regeneration results were not reproducible and their efficacy was limited. 2.- The company Aastrom Biosciences Inc. (Michigan, USA) initiated 2 phase I clinical trials in 2005. Five patients were treated with stem cells (Tissue Repair Cells) derived from bone marrow and mixed with BioOss matrix (deproteinized bone xenografs) in order to augment their maxillary sinuses before the placement of dental implants. Thirty-six patients with tibial fractures were also treated with autologous stem cells and demineralized bone matrix (DBM, MTF). The results of the pre-implant study proved the feasibility and innocuousness of the therapeutic approach, but the superiority of the resulting graft compared to the control (BioOss alone) could not be clearly demonstrated.

3.- In 2006, Springer and Nocini (Springer, Nocini et al. 2006), conducted a phase I-II controlled study in 5 patients investigating MSCs derived from the tuber maxilla, amplified in autologous serum and cultured on 8 mm^3 BioOss cubic scaffolds for 1.5 months that were then implanted for sinus augmentation. The results not only established the feasibility and innocuousness of the technique, with the implants being inserted after an 8-month healing period, but they also demonstrated the superiority of the bone tissue engineering method compared to the control group (BioOss alone).

4.- In 2008, Shayesteh (Shayesteh, Khojasteh et al. 2008) conducted a phase I study in 6 patients. Mesenchymal stem cells from BM were amplified in autologous serum then seeded on HA/TCP cubes (ratio 60/40, diameter 3 mm) 24 hours before being implanted for maxillary sinus augmentation. The results confirmed the innocuousness and feasibility of the technique but in the absence of a control group, the superiority of the hybrid material compared to the use of ceramics alone could not be proved.

The ImBioCeSM project aims at reconstructing edentulous and atrophied jaws in the posterior region using a combination of autologous mesenchymal stem cells (MSC) derived from BM and a synthetic microporous biphasic calcium phosphate (MBCP) bone substitute and a minimally invasive, standardized and safe surgical procedure. At the end of the bone healing period (approximately ~~9~~6 months), the implant site will be examined clinically and by X-ray before placement of the implants. A bone biopsy will be performed during the implant insertion procedure to assess bone neoformation.

Several technological issues related to the therapeutic approach still need to be addressed and will be assessed in the framework of the project, i.e.:

- maintenance of sterility and absence of contamination of the BM samples withdrawn in the various clinical centers,
- the logistics of distribution and the elevated cost of production,
- the non-reproducibility and difficulty in measuring the clinical efficacy of bone grafts,
- the protocol combining MSCs and the selected calcium phosphate ceramics must be validated in a preclinical model in terms of sterility before implant placement, innocuousness and efficacy.

1.1.2.Reminder of previous results

The osteoarticular and dental engineering Laboratory of the dental surgical Faculty of Nantes designs and assesses new matrices for tissue engineering, i.e. macroporous bioceramics, injectable bone substitutes, hydrogels. The multidisciplinary research conducted at the laboratory encompasses everything from the conception to the clinical application of biomaterials and new therapeutic approaches. The laboratory published the results of a clinical trial including 11 patients who were treated with an injectable bone substitute to fill their dental sockets (Weiss, Layrolle et al. 2007). Histological and histomorphometric analysis of the implant sites after 3 years showed that bone had grown back on contact with the calcium phosphate granules and that the alveolar ridge had been preserved, enabling the insertion of dental implants. A phase I multicenter clinical trial involving the reconstruction of osteoradionecroses by microporous biphasic calcium phosphate (MBCP+) and fresh BM cells is currently in progress at the Nantes University Hospital (Prof. Malard, ENT). The trial is based on research work that has been carried out at INSERM U791 by the Bone Engineering Group since 1998 (Jegoux, Aguado et al.; Jegoux, Malard et al.; Malard, Guicheux et al. 2005; Lerouxel, Weiss et al. 2006; Espitalier, Vinatier et al. 2009; Jegoux, Goyenvalle et al. 2009; Lerouxel, Moreau et al. 2009). Working in the laboratory between 2003 and 2009, Pierre Layrolle (DR2) and Jérome Sohier (PhD) developed a similar approach to bone engineering that is essentially centered on MSC – calcium phosphate matrix interactions. Several papers were published subsequent to this work (Sohier, Corre et al.; Le Guehennec, Goyenvalle et al. 2005; Le Nihouannen, Daculsi et al. 2005; Le Nihouannen, Duval et al. 2007; Le Nihouannen, Goyenvalle et al. 2007; Cordonnier, Layrolle et al. 2010).

The French Blood Institute (EFS) has implemented the production of clinical grade MSCs in the EFS Cell Therapy laboratories of the Center-Atlantic, Pyrenees-Mediterranean and Ile de France areas. A closed system production process based on the results of the graft group of the SFGM-TC (French Society for Bone Marrow Grafts and Cell Therapy) was developed by the EFS of the Center-Atlantic and Pyrenees-Mediterranean areas in partnership with the company Macopharma (national program of the RNTS [French National Technologies for Health Network] in 2004). The process that was validated by the AFSSAPS is used for the production of clinical-grade MSCS in compliance with GMPs (Sensebé, Bourin et al. 2006).

Several European clinical centers specialized in implant and pre-implant surgery joined forces for this project:

The Maxillofacial Surgery Department and the Medical School of Verona (UNIVR), directed by Prof. Nocini comprise several units implicated in the diagnosis and treatment of maxillofacial pathologies. The center is specialized in the following fields: endodontics, periodontics, oral surgery, temporomandibular joint dysfunction and oral cancerology. Several papers have been published as a result of the research activity of the center (Guerriero, De Santis et al. 1995; Nocini, Albanese et al. 2002; Nocini, De Santis et al. 2002; Springer, Nocini et al. 2006).

The Dental Clinical Research Center of the University of Bergen (UIB) directed by Profs. Ardvidson and Hellem is implicated in the fields of cell and vascular biology, biomaterials and bionanotechnologies, and in clinical research (Hellem, Karlsson et al. 2001; Hellem, Astrand et al. 2003; Arvidson, Esselin et al. 2008; Mustafa, Wennerberg et al. 2008).

The clinical activity of the Oro-dental-periodontics Surgical Department of the University of Liège (ULG-PARO) directed by Prof. Rompen, is strongly focused on

implantology. The department also conducts research on bone regeneration, periodontics and implantology (Rompen, Biewer et al. 1999; Rompen, Domken et al. 2006; Rompen, Raepsaet et al. 2007; Lambert, Lecloux et al. 2009; Lambert, Lecloux et al. 2010).

The field of expertise of the Implantology Department of the Dental Care Center of the Nantes University Hospital directed by Dr Hoornaert, is implant rehabilitation in patients with deficiencies (caused by traumatism or cancer). The clinical activity of the department focuses on periodontics, bone regeneration and implantology. The proximity of INSERM Unit 791 has facilitated the development of translational research (Le Nihouannen, Saffarzadeh et al. 2008; Roze, Babu et al. 2009; Saffarzadeh, Gauthier et al. 2009).

The Oral and Maxillofacial Surgery Department of the Nantes University Hospital (Prof. Mercier, Dr Perrin, Dr Huet, Dr Corre) is implicated in maxillofacial bone reconstruction (Ferri, Piot et al. 1997). Reconstruction is performed following traumatisms, cancer-related excisions or to rectify malformations. Since the advent of implant-borne dental rehabilitation, bone grafts have become essential for simple implant insertion in an ideal position to ensure prosthetic permanence (Ferri, Lauwers et al. 1997). Although the results of such reconstructions are indisputably good (they represent the gold standard in terms of management of bone deficiencies), some areas such as the posterior maxillary and mandible regions are still difficult to reconstruct. Reconstruction results are less consistent for these sites and the risk of resorption is elevated. Finally, and more essentially, the harvesting of bone grafts is associated with specific morbidity that should be taken into account. To avoid morbidity related to the withdrawal of bone graft samples, several biomaterials have already been used in other maxillofacial areas (Mercier, Piot et al. 1996; Malard, Espitalier et al. 2007), but with inferior results to the those obtained with autologous bone grafts. The purpose of this study is therefore to assess the results of bone reconstruction in a difficult area where, to date, no other techniques have demonstrated results equivalent to those obtained with autologous bone grafts. In the long run, the aim of the study is to replace bone grafts with a simpler and less invasive technique. Combining stem cells with a biomaterial in a biomimetic approach using a calcium scaffold and quota of active cells should produce results similar to those obtained with autologous grafts.

1.2.BENEFITS AND RISKS FOR THE PERSONS TAKING PART IN THE RESEARCH

1.2.1.Benefits

Individual benefit

Persons taking part in the research project will benefit individually from the placement of a dental implant without it being necessary for them to have an autologous bone sample taken from another site. Autologous sampling will be limited to the tapping of a few milliliters (ml) of BM under local anesthesia. This procedure is associated with less morbidity than that involving the removal of bone (less pain, less or no difficulty walking, no scars, very low risk of infection).

The benefit will be assessed:

- subjectively by the patients who will be asked to assess their pain and the difficulty they have walking and the intensity of the pain (Visual Analogue Scale, recording of the number of day(s) they experienced pain/difficulty in walking if the VAS >= 1),
- objectively by the physician during a medical examination: clinical examination of the harvest sight, inspection for any local complications.

Benefit for the population

From an economic viewpoint, it is logical to hope for a decrease in the estimated medical and social costs related to bone sampling thanks to decreased periods of professional inactivity (sick leave, leave without pay).

From a scientific viewpoint, researchers can expect to improve their knowledge of the procedures involving cell therapy and biomaterials, their efficacy and their innocuousness.

1.2.2.Risks

Individual risk

The risks connected with the procedure may involve the BM harvest site and the site of implant. Treatment failure (i.e. loss of the graft) is not considered to be a risk.

Risks related to the bone marrow harvest site (posterior superior iliac spine)						
Physical risks	Listed as: Certain, probable, possible, improbable, uncertain?	Directly related to the research?	Serious, or probably harmless?	Temporary or permanent?	Possibly painful?	Physically restrictive?
(1) Hematoma at the harvest site	Possible	Yes	Harmless	Temporary	Yes	No
(1) Persistent inflammation of the harvest site (> or = 7 days under treatment)	Possible	Yes	Harmless	Temporary	No	No
(1) Local bleeding (< or = 1 day): compressive dressing may be required	Improbable	Yes	Harmless	Temporary	Yes	No
(1) Burning sensation for 48 h	Possible	Yes	Harmless	Temporary	Yes	No
Local infection at the harvest site	Possible	Yes	Harmless	Temporary	Yes	No
(1) Residual pain after 48 h: generally regresses with level 1 analgesics	Possible	Yes	Harmless	Temporary	Yes	Yes
(1) Temporary functional lameness of the legs: difficulty walking for 48 h	Possible	Yes	Harmless	Temporary	Yes	Yes
Rupture of the trocar needle	Improbable	Yes	Serious	Temporary	Yes	Yes

(1) As these events are normally expected following such a procedure, it was decided not to report them in as AEs in the patient case report forms; they must however still be reported

Risks related to the implant site (posterior region of the jaw)						
Physical risks	Listed as: Certain, probable, possible, improbable, uncertain?	Directly related to the research?	Serious, or probably harmless?	Temporary or permanent?	Possibly painful?	Physically restrictive?
Inflammation for several weeks (notably because of the onlay membrane)	Probable	Yes	Harmless	Temporary	No	No
(1) Postoperative edema (> or = 7 days under treatment)	Possible	Yes	Harmless	Temporary	Yes	No
(1) Postoperative bleeding (> or = 1 day)	Possible	No	Harmless	Temporary	No	No
Persistent pain (more than 3 weeks) at the implant site requiring increased doses of analgesics compared to normal requirements	Possible	Yes	Harmless	Temporary	Yes	Yes
Superficial gingival infection, potentially worsened by the onlay membrane	Possible	Yes	Serious	Temporary	Yes	No
Local infection at the implant site	Possible	Yes	Serious	Temporary	Yes	No
Migration of the biomaterial along the length of the alveolar bone on both sides of the reconstructed area	Probable	Yes	Serious	Temporary	No	Yes
Healing disorders (mucosal disunion)	Possible	No	Serious	Temporary	Yes	Yes
Elimination of the graft	Possible	Yes	Serious (withdrawal from the study)	Temporary	No	Yes
Any event linked to the local or general anesthesia (allergy, malaise, etc.)	Possible	No	Serious	Temporary	No	Yes

(1) As these events are normally expected following such a procedure, it was decided not to report them in as AEs in the patient case report forms; they must however still be reported

- Risks related to the study treatments and concomitant treatments (AEs)

The risks are those usually associated with oral surgery and BM sampling. The non-exhaustive list of AEs is provided in the pharmacovigilance section (see below).

- Psychological risks and constraints

The handling of cells in the context of cell therapy (sampling, amplification, reintroduction into the organism) may result in numerous questions being asked by the patients and may, to a certain degree, generate anxiety. The patients will be given clear and accurate information about the procedures performed at each step of the process.

- Socio-economic risks

No socio-economic risks are envisaged for the patients as the need for implants will be defined and accepted by the patients prior to their inclusion in the study and the procedures that are specific to the study will be paid for.

Nonetheless, an additional operating procedure for the harvesting of bone marrow is scheduled in the study, but the procedure will be paid for (specialist consultation and sampling material cost overruns).

Risk for the population

Not envisaged.

1.2.3. Benefit / risk ratio

The benefit/risk ratio of this study appears favorable for several reasons:

There are fewer undesirable effects and specific risks associated with BM withdrawal than with the harvesting of bone for autologous implants.

It can be supposed that the benefits of the biomaterial graft seeded with MSCs will be equivalent or superior to those of a graft of biomaterial alone as shown in several clinical studies.

No deleterious effects specific to autologous MSCs have ever been detected during their use in clinical trials involving humans, although they are systematically checked for.

Apart from the trocar needle rupturing during bone marrow sampling which is unlikely to occur, the other risks are not dangerous and are temporary, and most of them are not physically restrictive.

Moreover, the constraints are non-invasive and relatively non-restrictive compared to those endured in cases of autologous grafts.

1.3. DESCRIPTION AND RATIONALE FOR THE THERAPEUTIC PROTOCOL

1.3.1. Biomaterial used: MBCP+ (Biomatlante, Vigneux de Bretagne, France)

The bone substitution material selected is a biphasic micro/macroporous calcium phosphate (MBCP+™) class III medical device (code GMDN 17751) that is implantable and inactive, marked CE 123 and FDA, and used for its indication (Class III medical device for long term implantation used for bone filling in traumatology, orthopedics and spinal surgery and for fractures with bone loss), marketed in the form of granules by Biomatlante (Vigneux de Bretagne, France). The material is used in humans in the clinical setting for a variety of indications such as orthopedic surgery, otorhinolaryngology or dentistry (Malard,

Espitalier et al. 2007). The diameter of the granules is between 1 and 2 mm. Physicochemical analysis of the granules shows a hydroxylapatite (HA) and triphasic calcium phosphate (β-TCP) ratio of 20/80, the 2 phases are mixed intimately at the molecular scale, forming the same crystalline unit. The HA/β-TCP 20/80 ratio was selected because of its bone forming properties (Arinzadeh TL, Tran T, McAlary J, Daculsi G. A comparative study of biphasic calcium phosphate ceramics for human mesenchymal stem-cell-induced bone formation. Biomaterials. 2005 Jun;26(17):3631-8.) and its efficacy in terms of implant resorption and simultaneous substitution by natural, regenerated, structured and vascularized bone.
The macropores are 300 to 600 µm in size and have an overall porosity of 80% (macroporisity: 80 %, microporosity 20 %). Porosity is an essential physical characteristic of MBCP+. Microporosity (pores smaller than 10 µm) is essential for circulation and humoral and ionic exchanges, while macroporisity plays a role in cell colonization. The chemical composition of MBCP+ is similar to the mineral phase of bone, which gives it the following properties: biocompatibility, osteoconduction, osteogenicity, biodegradability and biofunctionality, making it the ideal material for bone regeneration.
Osteocondution is the capacity of the material to serve as a support structure for bone growth. Because of its structure, MBCP+ serves as a scaffold for newly formed bone tissue. The macroporisity of the material favors its colonization by osteogenic precursor cells, particularly their adhesion and proliferation. The microporosity of the material renders it bioactive. It improves the interactions between the material and the biological environment, notably the release of calcium and phosphate ions, which enables differentiation of osteogenic precursor cells and precipitation of biological apatite that is recognized by the bone cells of the receiver. By a mechanism of bone remodeling [that complies with the BMU (Bone Morphogenic Unit, Frost's theory) in bone pathophysiology], the material is then progressively resorbed and replaced by newly formed, vascularized bone tissue. All these phenomena guide the bone healing process.
MBCP+™ is supplied ready for use, in special syringes in order to facilitate and control the addition of bone marrow cells or tissue engineering derivatives such as MSCs that augment the material's osteoinduction properties, in sterile packaging. The MBCP+™ medical device is sterilized by irradiation at 25 Kgrays, making it suitable for surgical use.
See Appendix?? MBCP+ TM User guide.

1.3.2. Bone marrow harvest

10 to 15 ml of BM will be withdrawn in a standardized manner under local anesthesia from the posterior superior iliac spine in compliance with a protocol established by the maxillofacial and orthopedic clinical investigating centers according to the recommendations published by the French Hematology Society (SFH), the French Cell Hematology Group (CFHC), the Hospital Hematology Board (CHH) and the French National Union for Hospital Biologists (SNBH) (Appendix X). Once it has been withdrawn, the BM will be placed in a refrigerated container and dispatched by a special road courier service to a cell therapy center that has been accredited for level 3 manipulations (open system manipulations) by the AFSSAPS (French Health Products Safety Agency) or the corresponding regulatory authority in the countries participating in the clinical trial.

1.3.3. Cell culture

The BM will be controlled once it arrives in the cell therapy center: the total amount of nucleated cells will be assessed, a myelogram established, a bacteriological test performed and the initial number of CFU-F cells assessed. The BM will then be cultured using a process that produces clinical-grade MSCs developed by the EFS (Bourin and Sensebé 2005). CellStacks-type (Corning, USA) containers will seeded with 1x103 nucleated primary cells per cm² in a closed system. The culture medium will consist of MEMα and allogeneic human plasma enriched with platelet gel (containing growth factors) developed by the EFS i.e. an allogeneic preparation that produces better results than the fetal calf serum generally used and that allows safe production of MSCs for clinical use. The culture medium will be changed every 2 days. With the MSC culture methods developed by the EFS, the cells are only passaged once so that they may retain the functional characteristics of MSCs although the passaging allows a sufficient amount of cells to be produced for a surgical procedure. The MSCs will then be detached, counted and suspended in a 4% human albumin solution (Vialebex; Code ATC : B05AA01, Laboratoires LFB BIOMEDICAMENTS http://www.has-sante.fr/portail/jcms/c_493569/ct-4072) at a concentration of 10 to 20 million cells per ml. The resulting mixture or cell therapy product (CTP) will be filled into 10 ml Luer

lock syringes and placed in sterile packaging before being dispatched to the clinical center by an express road courier service. The sampling, culture and packaging of the BM cells will be conducted under aseptic surgical conditions. The MSCs will be only be used for patient grafts if the final results of the initial and intermediate bacteriological tests are negative. The results of viral tests, that are identical to those performed in the framework of hematopoietic stem cell transplantation, must be negative. The absence of bacteriological risk related to the culture procedure will also be checked for by carrying out a bacteriological study that meets the criteria defined by the AFSSAPS on the cells at various culture times. Process and production controls will also be carried out on the CTP, i.e.:

• Sterility of the contents of the syringes after a duration equivalent to 6 hours of transport at 4°C,

• Production process (viability, expansion ratio, phenotypic study by flow cytometry (absence of expression of hematopoietic markers (CD45, CD14 and CD34) and presence of the main markers of MSCs (CD73 et CD90 (+/- CD105 or CD49a)),

• production tests before the cells are used in patients, particularly that demonstrate the *in vivo* functionality of the MSCs using a relevant animal model, i.e. validation of the biological effect of the CTP in a mouse model at ectopic and orthotopic sites.

1.3.4.The MBCP+ and MSC combination

The protocol used to combine the MSCs with biomaterials is mainly based on preclinical studies performed by Mankani in 2007 (Mankani, Kuznetsov et al. 2007). The author showed that ectopic bone formation in mice using a mixture of calcium phosphate and human MSCs was proportional to the quantity of cells seeded on the biomaterial. Approximately 7500 cells per milligram (mg) of material was found to be the optimal ratio.

Based on the above findings, the Reborne consortium chose to associate between 2000 to 4000 cells per mg of material, i.e. a volume ratio of 0.5 to 1 ml of cells resuspended in albumin for 1 ml of biomaterial (approx. 500 mg).

The material will be filled into sterile syringes of different volumes (1 to 5 ml). The choice of volume will be adapted to each patient and defined beforehand, at the time the bone graft procedure is planned, as a function of the volume of bone loss observed.

The MSCs will be mixed with the material immediately before use under aseptic surgical conditions by the clinician performing the pre-implant surgery.

The syringe containing the CTP will be removed from its sterile package by the surgeon. An 18-gauge needle (pink) will be attached to the syringe. The needle will then be pushed through the membrane seal of the syringe containing the biomaterial until the end stop is reached. The cell suspension will be injected towards the back so that as many as possible of the granules are impregnated. The needle will then be removed and the plunger of the syringe containing the biomaterial will be depressed. The syringe containing the mixture will then be allowed to stand in a sterile environment (equivalent to risk area level 3 corresponding to the norm AFNOR NF 50-790, high infectious risk level, not classified regarding particle standard) at room temperature throughout the surgical procedure (i.e. at least 1 hour). When it is time to insert the graft, the cap of the syringe will be unscrewed and the seeded material will be withdrawn directly from the syringe using a spatula and immediately placed in the implant site.

Part of the mixture will be preserved to perform additional analyses, particularly bacteriological tests, to confirm the sterility of the mixture after 1 hour of contact between the biomaterial and the MSCs.

1.3.5.Pre-implant surgical procedure (annex 5)

The surgical procedure will be standardized for each clinical center:

Prevention of bacterial contamination:

a. Start of antibiotic treatment the day before the procedure (Amoxicillin 3 g/d orally, or Clindamycin 600 mg X 3/d)
b. Brushing of teeth and mouthwash with Chlorexidine or equivalent in the hour prior to surgery
c. Surgical area aseptically bathed with Chlorexidine or equivalent by the surgeon
d. Setting up of a sterile field around the oral cavity.

Anesthesia

e. Local anesthesia: the surgical area will be systematically anesthetized by submucosal infiltration of adrenalized Xylocaine (1% epinephrine) or articaine hydrochloride (Spad)
f. General anesthesia: it will be proposed to patients requiring extensive reconstruction or who are extremely anxious.

Exposure of the area to be reconstructed

g. The incision will correspond specifically to the surgical area.
h. ~~Maxillary region behind the canine teeth~~
   i. Mandible region behind the canine teeth
i. Incision/detachment:
   i. ~~Maxillary region behind the canine teeth: a full-thickness incision is performed on the top of the crest, from the distal part of the remaining mesial tooth to the mesial part of the distal tooth. Mesially and distally, the incision is extended to the distal part of the remaining tooth. A releasing incision is performed backwards and vertically to the free gingival. If necessary a releasing incision can be carried out in mesial part of the defect. The surgical area is scrapped under the periosteum to expose the whole of the ridge to be reconstructed. A slight detachement is made on the palatine or lingual side to fix the membrane to prevent a sliding of the biomaterial.~~

Abrasion of the bony ridges

The cortical bone will be perforated using a fine round bur to favor the flow of blood into the biomaterials.

Placement of the biomaterials

The regenerative membrane will be fixed to the underlying bone by surgical non absorbable nails and held in place on the gum by resorbable sutures if necessary. First the lingual side of the membrane at the mandible ~~(or the palatal side at the maxillary bone)~~ will be attached to the jaw. Then the vestibular side of the membrane will be fixed distally to create a opened channel. The vestibular and mesial side will be left free so that the biomaterial may be introduced into the resulting pocket.

After the cap of the syringe containing the biomaterial has been unscrewed, the material will be withdrawn using a spatula and introduced into the pocket formed by the bony ridge and the regenerative membrane. The remaining biomaterial will be preserved to perform additional analyses.

Once the biomaterial is in place, the last side of the regenerative membrane will be attached to the bone or sutured in the submucosal plane on the vestibular side.

Closure of the surgical wound

j. The vestibular mucosa will be expanded thanks to an incision of the periosteum providing a muco-periosteal flap that covers the membrane without tension.
k. The muco-peritosteal flap will be sutured to the vestibular mucosa in 2 planes if possible (submucosal and mucosal) using non-resorbable sutures (5/0 synthetic absorbable mono filament suture).
l. The surgical area will be cleansed with saline solution.

Postoperative care and monitoring

m. The procedure does not require hospitalization if it is performed under local or loco-regional anesthesia. In cases of general anesthesia, the patient will be hospitalized for one or two days.

Treatment:

   i. Local: the teeth must be brushed with a post-surgical toothbrush and mouthwashes performed as from the evening after the procedure.
   ii. General: antibiotic treatment with Amoxicillin or Clindamycin continued for 7 days. Pain treated with paracetamol 1g X 4/D. In cases of more intense pain, paracetamol 1 g will be replaced by a level II analgesic.

n. Hygiene-dietary recommendations
   i. Smoking and wearing of a denture that presses on the operated area will be contraindicated throughout the time it takes for the bone and mucosa to heal.
   ii. The patient will be advised to eat soft, warm foods for 7 days.
   iii. The patient will be encouraged to apply ice to the cheek on the side of the operation continually during the first 48 hours after surgery.
   iv. Chewing on the operated side must be limited for the duration of the bone healing process (i.e. 6 to 9 months)

o. Post-operative consultations
   i. The first visit will take place 7 days after surgery except in the case of an intercurrent event and will include a clinical and radiological examination of the operated area. The sutures will be removed.
   ii. The second visit will take place 1 month after the operation (M1). It will consist in only a clinical examination.

1.3.6.Implant surgery

1.3.6.1. Implants:

The implants selected by the clinicians for the study are bone level Regular CrossFit™ implants manufactured by Straumann® or similar (-bone level **standard implants** (Straumann, Nobel, etc) with the **same diameter and length)**

Specific indications for Straumann® Bone Level implants

Implant type		Indications and distinctive features	Minimal ridge width*	Minimal gap width**
BL Ø 3.3 mm NC		■ Small diameter implant for narrow interdental spaces and ridges ⚠ **Caution** Placement in the molar region is not recommended	5,5 mm	5,5 mm
BL Ø 4.1 mm RC		■ For oral endosteal implant indications in the maxilla and mandible, for functional and esthetic rehabilitation of edentulous and partially edentulous patients	6 mm	6 mm

~~There is sufficient clinical perspective with Straumann® implants for them to be employed in the project and they are currently used by the 4 centers participating in the study.~~
The bone level type implants were selected because of the reliability of the healing method in two stages that should allow better integration of the implant in the grafted biomaterials.

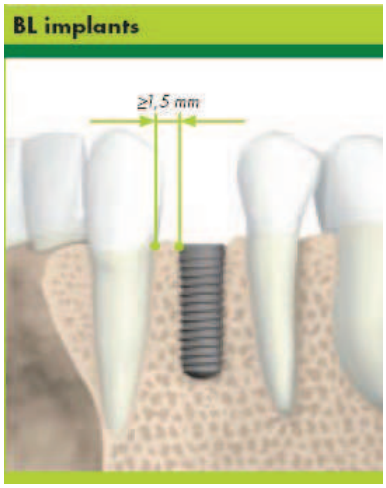
Additional information can be obtained on the manufacturer's site at the following addresses:
http://www.straumann.fr/fr-index/products/products-surgical-bone-level/products-bone-level.htm
http://www.straumann.fr/15x_754_surgical_procedure.pdf

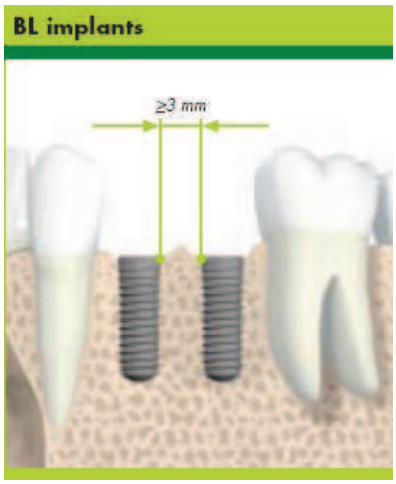
The dimensions of the implant used in the study are as follows:
- Diameter = 4.1 mm
- Length = 10 or 12 mm

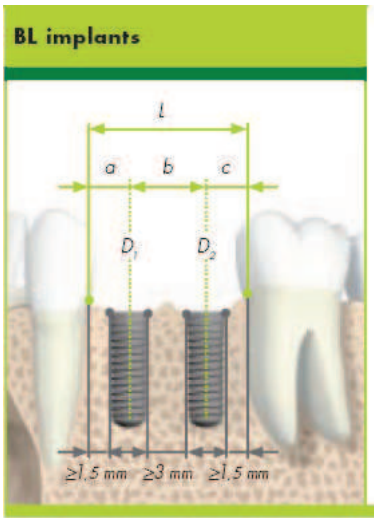
1.3.6.2. Surgical procedure

During the surgical procedure, the implants will be placed in the mesiodistal, orofacial and coronoapical positions according to the manufacturer's recommendations.

a. **Mesiodistal implant position**: a minimal distance of 1.5 mm from the implant shoulder to the adjacent tooth at bone level and a distance of 3 mm between two adjacent implant shoulders is required (mesial and distal).







Implant diameter D_1 (mm)	Implant diameter D_2 (mm)	a_{min} (mm)	b_{min} (mm)	c_{min} (mm)	L_{min} (mm)
BL Ø 3,3	BL Ø 3,3	3	6,5	3	12,5
BL Ø 3,3	BL Ø 4,1	3	7	3,5	13,5
BL Ø 3,3	BL Ø 4,8	3	7	4	14
BL Ø 4,1	BL Ø 4,1	3,5	7	3,5	14
BL Ø 4,1	BL Ø 4,8	3,5	7,5	4	15
BL Ø 4,8	BL Ø 4,8	4	7,5	4	15,5

Key to above table:

Implant diameter D1 (mm) **Implant diameter D2 (mm)**

b.Orofacial position of the implant: the minimal orofacial ridge width for the selected implant is 6 mm

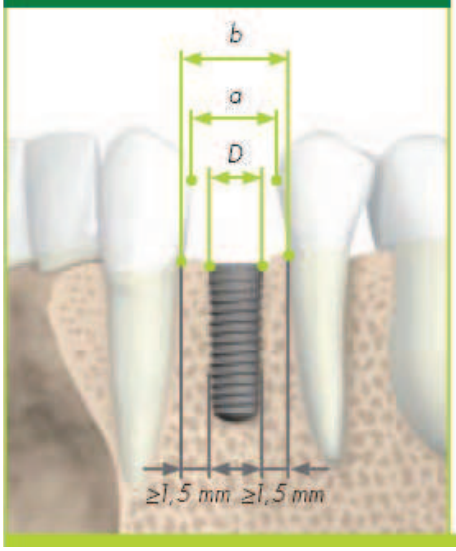
.

Key to above table:

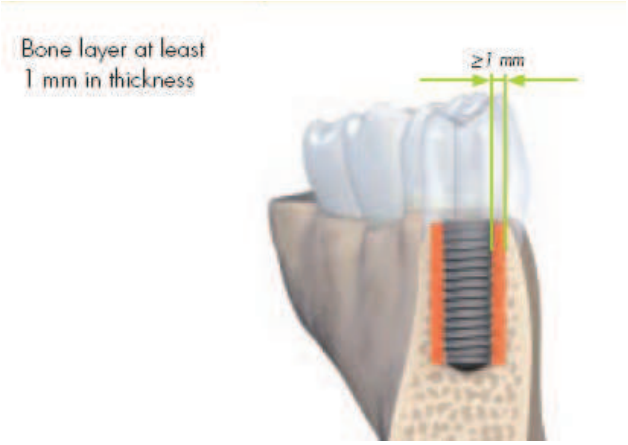
Specific indications for Straumann® Bone Level implants

Type of implant	**Indications and distinctive features**
BL Ø 4.1 mm RC:	For oral endosteal implant indications in the ~~maxilla and~~ mandible, for functional and esthetic rehabilitation of edentulous and partially edentulous patients
Minimal ridge width*	6 mm
Minimal gap width**	6 mm

BL implants



Implant diameter D (mm)	Gap width a_{min} (mm)	Distance between adjacent teeth at bone level b_{min} (mm)
BL Ø 3,3	5,5	6,5
BL Ø 4,1	6	7
BL Ø 4,8	7	8
Rule	D + 2 mm	D + 3 mm*



c. Coronoapical position of the implant

Bone Level implants are best set with the outer rim of the small 45° sloping edge (chamfer) at bone level. In a scalloped situation, place the mesial/distal point of the outer rim of the implant at bone level. The lingual/palatinal wall will then extend slightly over the top line of the implant. The buccal wall is located somewhat below the implant edge.

2. OBJECTIVES AND EVALUATION CRITERIA

2.1. PRINCIPAL OBJECTIVE AND EVALUATION CRITERION

2.1.1. Principal objective

The principal objective is to assess whether or not it is possible to insert an implant in the reconstructed area 96 months after the graft. The decision will be made based on radiological and clinical examinations.

2.1.2. Principal assessment criterion

Whether or not it is possible to insert an implant is based on **radiological and clinical results**.

- **Radiological examination**: Initial height of the ridge + height of the graft greater than or equal to the length of the implant

AND initial width of the ridge + width of the graft greater than or equal to the diameter of the implant + 2 mm (1 mm safety margin on each side)

AND absence of disorders contraindicating the insertion of the implant visible on the scan, i.e.: sinusitis, osteitis…

AND

- **Clinical examination:**

Absence of inflammation or local or general infection preventing the placement of the implant (in addition to other general contraindications)

At the end of the study, the medical results for all patients included will be reviewed by four investigators (1 for each centre) to asses the clinical and radiological data relevance.

2.2. SECONDARY OBJECTIVES AND EVALUATION CRITERIA

2.2.1. Secondary objective(s)

The following secondary objectives will be assessed based on:

Clinical results

Subjective clinical appraisal of the quality of the newly formed bone after incision of the mucosa before implant placement (using the Likert scale)

Implant stability measurement the using the Ostell /ISQ system

Pain, scar, functional limitations

Potential procedure- or study-related complications

Radiological results

Height and width of the reconstructed ridge

Quality of the newly formed bone (centralized biopsies analysis)

Histological results

Qualitative / quantitative assessment of the newly formed bone(centralized biopsies analysis)

2.2.2. Secondary evaluation criteria

See above comments

2.3. OBJECTIVES AND EVALUATION CRITERIA OF ANCILLARY STUDIES

Irrelevant

3. RESEARCH PLAN

3.1. GENERAL METHODOLOGY

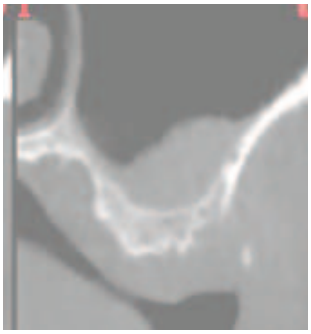
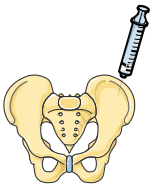
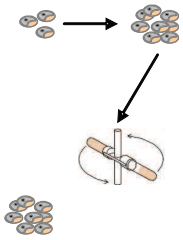
The research project has the following characteristics: multicenter, international, uncontrolled prospective cell therapy study.
It was decided to conduct the study according to a non-comparative experimental design because the study procedure is a complex, non-pharmacological procedure that will be part of the learning curve of the operators involved. Thus, the study can be compared to an early phase medicinal study and it will be followed by a randomized study to continue investigation of the therapeutic approach if the results observed are encouraging.

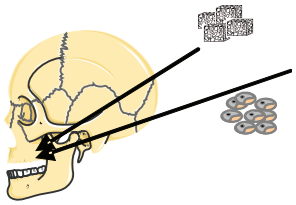
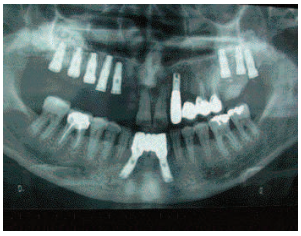
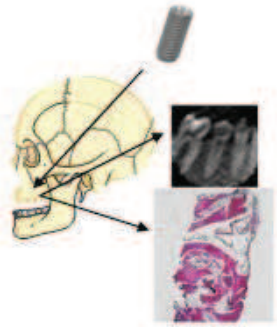
3.2. STUDY DESIGN

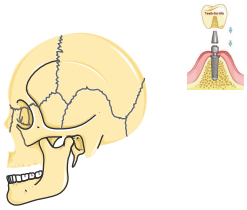
Control group depending of the literature review concerning the success of lateral augmentation in mandible with biomaterial solely

– If material doesn't work : Cells and material on both sides

– **If material can support a slight bone formation**: **split mouth** study one side with material /one side with material and cells? Should the unit be 1 patient or 1 area ?

A. Subject selection D-45 – D-16 	The patients will be selected by means of a radiological examination (cone beam CT imaging or low dose CT scan) with radiological guide to confirm bone loss behind the canine teeth of the mandible ~~or maxilla~~, requiring an onlay bone graft. The patients requiring a bone graft will be asked if they wish to test the procedure involving biomaterials and stem cells as an alternative to the reference procedure.
B. Inclusion 	Checking of the inclusion and exclusion criteria by the maxillofacial surgeon or dentist. Information provided to the patient and free, informed consent obtained from the patient.
C. Sampling of stem cells D-15 	15 ml of bone marrow will be withdrawn by the surgeon from the posterior superior iliac spine under local anesthesia and packaged by a person with the right competences and familiar with Good Laboratory Practices (GLP) in the maxillofacial or orthopedic operating area depending on the centers. The sample will be preserved with dry heparin and shipped immediately by special transport to one of the local laboratories participating in the study in compliance with the terms agreed on by the partners.
D. Production of MSCs D-15 – D0 	The Cell Therapy laboratories will check the quality of the initial bone marrow sample and will undertake to produce MSCs using the samples on condition that they meet quality requirements (state of the cells, number of cells, etc.). The Cell Therapy laboratories will also ensure that the final cell therapy product (CTP) is returned to the center by special transport on the day of the graft.
E. Bone filling with the	The receiving site on the mandible ~~or maxilla~~ will be prepared for filling with the hybrid

hybrid biomaterial = D0 – M0 	biomaterial consisting of BCP granules and autologous mesenchymal stem cells (cells from the patient cultured *in vitro*). The CTP will be applied to the biomaterial *in vivo*, in the operating area, 60 minutes before it is used to reconstruct the bone defect. The bone substitute filled into syringes and sterilized by gamma irradiation will be provided by Biomatlante SAS. The bone substitute will be combined with a suspension of autologous mesenchymal stem cells (MSC) immediately before use (10 x 10^6 MSC / 1 ml human albumin at 4%). The bone site will be covered by a resorbable collagen membrane that will form a pocket into which the biomaterials will be introduced and that will limit the proliferation of conjunctive gum tissue at the site of the graft. The 30 x 40 mm collagen membrane of animal origin is provided by Biomatlante SAS. A radiological examination (low dose CT scan or cone beam CT imaging) will take place 7 days after bone reconstruction.
F. Biopsy sampling and dental implantation M69  	At the end of the healing period (96 months), radiological and clinical examinations will be performed to determine whether or not the patient may have one or several implants inserted. The assessment criteria are detailed in section 2.1.2. If it is possible to insert an implant based on the clinical and radiological examinations, the procedure will take place in 2 stages. 1. Bone biopsy The biopsy will be performed in an operating theater under aseptic surgical conditions and local or loco-regional anesthesia. The mucosa of the implant area will be infiltrated with adrenalized Xylocaine (1% epinephrine) or articaine hydrochloride (Spad). The mucosa will be incised crestally, and then scraped in the subperiosteal plane to expose the bony ridge. The histological sample will be taken from the graft at the site of the implant using a serrated trephine and an extractor. The drill guide will be placed to enable drilling vertically along the axis of the implant or transversally in cases of lateral augmentation of the bony ridge. In cases where drilling is vertical, the hole will be drilled in the center of the future hole of the implant to limit bone loss at the site. The diameter of the core sample will depend on the size of the implant planned. The biopsies will be placed in a fixing bath (4.8% neutral formaldehyde) immediately after sampling and sent the cytopathology department in Nantes for preparation and histological analysis (centralized analysis). Each sample will be analyzed by an anatomopathologist of the Nantes University Hospital during a centralized reviewal procedure. 2. Dental implantation The hole for the implant will be drilled immediately after the biopsy has been taken using the drill guide. Drilling and implant insertion will be carried out following standard surgical implant practices. Once the implant has been inserted, its primary stability will be assessed using Resonance Frequency Analysis (RFA, Osstell). A closure screw will be inserted and the surgical site cleaned and sutured with absorbable sutures. Postoperative care is described in detail in section 1.3.5.6. A retroalveolar examination will be performed in the postoperative period to check the position of the implant.
G. Insertion of the healing cap M9~~12 – M15~~	At the end of the osseointegration period of the implant (3 months) ~~for the mandible and 6 months for the maxilla),~~ the gum will be incised directly above the implant under short local anesthesia and aseptic surgical conditions. The healing cap will be inserted once the implant head has been exposed. An X-ray will be made of the implant and its stability assessed by Resonance Frequency Analysis (RFA, Osstell). The gum will be sutured around the healing cap with resorbable sutures. Postoperative treatment includes simple analgesics and mouth care

H. Loading of the implant M~~139 (or M10) – M16~~ 	The implant may be loaded either at the time the healing cap is inserted or a few weeks later, depending on the habits of the clinical teams. The procedure will be conducted according to standard practices in a dental treatment room.
I. Long-term follow-up M24 	Clinical and radiological follow-up is programmed up to 24 months after the graft. It includes subjective satisfaction assessment, a clinical examination, implant stability measurement by Resonance Frequency Analysis and a retroalveolar radiography.

4. STUDY POPULATION

4.1. DESCRIPTION OF THE POPULATION

Forty patients will be included in the study (see justification of the number of subjects required in the "Statistics" section), i.e. both men and women aged 18 years or more, offered bone reconstruction prior to implant placement in one of the clinical departments participating in the study.

The persons participating in the study will not be able to simultaneously participate in another trial unless it is a strictly observational or retrospective study. No exclusion period has been scheduled at the end of the study.

4.2. PRE-INCLUSION CRITERIA

Men and women aged 18 years or more requiring jaw bone reconstruction prior to dental implant placement based on clinical and radiological examinations (CT scan or cone beam CT imaging).

Areas suitable for reconstruction correspond to the ~~maxillary or~~ mandible areas behind the canine teeth affected by lateral or vertical bone loss (focusing lateral bone loss) and including a posterior tooth. Patients must be beneficiaries of the French Social Security or a similar insurance system. They must receive clear information about the study and give their free consent to participate in the study.

4.3. INCLUSION CRITERIA

Local criteria:

- Patients presenting with an indication for an implant and wanting implant-borne prosthetic restoration.
- Patients presenting with lateral or vertical bone loss (focusing lateral bone loss) ~~loss~~ of the mandible ~~or maxilla~~ behind the canine tooth, with at least one residual tooth in posterior region.
- Lateral (width < 6 mm) ~~or vertical (height < 10 mm)~~ bone loss preventing the insertion of an implant without prior bone augmentation.
- Edentulousness for more than 6 months in the region requiring reconstruction.
- Edentulousness concerning at least 2 missing teeth (with or without a remaining tooth) ~~1 or more teeth~~ in the region requiring reconstruction.
- Absence of clinical signs of infection in the region requiring reconstruction.
- Patients presenting with good dental hygiene
- Patients not presenting with any major oral pathologies.
-
- Dental crest size = 2-4 mm

General criteria:

- Adult patients over 18 and under 80 years of age.
- Patients in good general health presenting with a complete blood count and renal and hepatic function values within normal limits (confirmed by local laboratory tests).
- Patients with the capacity to understand medical information and give their informed consent.

4.4. EXCLUSION CRITERIA

Local criteria:

- Patients presenting with clinical or radiological signs of bone or sinus infection (acute or chronic osteomyelitis~~, acute or chronic maxillary sinusitis if maxillary reconstruction is required~~).
- Residual dentition close to the area requiring reconstruction with untreated endodontic disorder (apical granuloma or apical cyst).
- Untreated oral infection (cellulitis, periodontitis).
- Patients with poor hygiene.
- Surgical procedure undertaken in the area requiring reconstruction less than 6 months prior to the bone graft.
- History of malignant tumors of the upper airways / digestive tract or of the jaw.
- History of or scheduled cervico-facial radiation therapy.

General criteria:

- Patients presenting with bone metabolism disorders: hypophosphatemia, primary parathyroid osteitis or that is secondary to chronic renal insufficiency or osteomalacia, Paget's disease, vitamin D-related disorders, osteoporosis.
- Pregnant or breastfeeding women or women not using effective contraception if they are of childbearing age.
- Patients presenting with cancerous disorders (carcinoma, sarcoma, leukemia, lymphoma) or psychiatric disorders or with uncontrolled systemic diseases (diabetes, hypertension), or chronic renal disease.
- Severe bruxism.
- History of chemotherapy.
- Smoking or alcohol addiction. Occasional consumption of alcohol and/or smoking will be noted in the case report form.
- Patients with an ASA score of 0 or 1, incapable of tolerating general anesthesia.
- Glasgow Score < 13
- Allergy to proteins contained in the products of animal origin (horse, veal, pork) required during the study.
- Allergy to the constituents of the local anesthesia (sulfites, etc.).
- Immunosuppression
- Body mass index outside the normal range, particularly > 25 because of increased surgical risk at the time of BM harvesting from the iliac spine.
- Risk of remote infection (orthopedic prosthesis implanted in the previous 6 months, patients presenting with a high risk of infective endocarditis, presence of pulmonary arteriovenous shunt, etc.).
- HIV, HTLV and/or syphilis seropositivity.
- Hepatitis B or C infection.
- Active autoimmune disease.
- History of immunosuppressant treatment or bone marrow treatment.
- Administration of treatment interfering with bone metabolism.
- Patients requiring antibiotic prophylaxis before any dental procedure
- Patients reticent to undergo dental care or periodontal treatment
- Patients presenting with blood coagulation disorders
- Concomitant treatments: history of treatment or current treatment with bisphosphonates, long term corticosteroid treatment.
- Minor(s) or persons of full age under tutorship.

5. TREATMENTS USED DURING THE STUDY

5.1.1.Calcium phosphate bone substitute (MBCP+)

Today, bone surgery often involves autologous bone grafts and the use of bone substitutes. Bone substitutes were developed to avoid the problems associated with grafts in terms of morbidity of the harvest site and excessive resorption (Malard, Espitalier et al. 2007). Calcium phosphate substitutes such as biphasic calcium phosphate ceramics have been widely studied and are useful for bone reconstruction in orthopedic, maxillofacial and otorhinolaryngology surgery. They are marked with the CE stamp, are accredited as level III medical devices by the FDA and are widely commercialized (Daculsi, Laboux et al. 2003). The very good osteoconductive properties of the biomaterials used alone have been extensively demonstrated in orthopedic and maxillofacial surgery, but they are insufficient for reconstructing large bone defects or defects with low healing potential. Thanks to optimization of the microstructure of biphasic calcium phosphate micro and macroporous bioceramics, these materials demonstrate bone forming properties rarely observed with other calcium phosphate substitutes (Le Nihouannen, Daculsi et al. 2005). Osteoinduction is the capacity to form bone in an ectopic site (non-bone site). Consequently, combining optimized scaffolds with osteogenic precursor cells is the surgical solution of the future. The host's stem cells are collected and their differentiation into osteogenic precursor cells is favored by the material. It has been suggested that adult cells of varying origins (mesenchymal or fatty tissues, etc.) be used for the purpose of osteoinduction.

5.1.2.Cell therapy product

5.1.3.Hybrid material

The bone substitution material selected is a biphasic micro/macroporous calcium phosphate (MBCP+™) class III medical device (code GMDN 17751) that is implantable and inactive, marked CE 123 and FDA, and used for its indication (Class III medical device for long term implantation used for bone filling in traumatology, orthopedics and spinal surgery and for fractures with bone loss), marketed in the form of granules by Biomatlante (Vigneux de Bretagne, France). MBCP+™ is supplied ready for use, in special syringes, in sterile packaging. The MBCP+™ medical device is sterilized by irradiation at 25 Kgrays, making it suitable for surgical use.
It is mixed with the cell therapy suspension in an albumin – biomaterial ratio of 0.5 to 1 for 1. The material is packaged into sterile syringes: each syringe contains 5 ml of 1-2 mm granules (5 ml of granules per 7 ml of cell suspension). The cell suspension will be mixed with the material immediately before use, with no prior albumin impregnation of the granules, under aseptic surgical conditions by the clinician performing the pre-implant surgery.
An 18-gauge needle will be attached to the syringe containing the cell suspension. the plunger of the syringe containing the biomaterial will be depressed before inserting the needle and the cell suspension for better impregnation.The needle will then be pushed through the membrane seal of the syringe containing the biomaterial until the end stop is reached. The cell suspension will be injected towards the back so that as many as possible of the granules are homogeneously impregnated with the cells. The needle will then be removed. The syringe will then kept immobile in a sterile environment at room temperature for 1 hour. When it is time to insert the graft, the cap of the syringe will be unscrewed and the seeded material will be withdrawn directly from the syringe using a spatula and immediately placed on the site requiring reconstruction.

5.1.4.Tissue regenerating membrane

EZ Cure is a porcine-derived microstructured cross-linked collagen membrane that has been highly purified for added safety and tissue compatibility, combining resorption control and flexibility. Ez Cure, produced through a novel extraction and shaping process, is supple, pliable, easy to handle and can be adapted to varying bone geometries.

EZ Cure acts as a barrier for at least 3 months, preventing conjunctival or epithelial cells from colonizing the surgical site during healing. The cross-linked technology optimizes the barrier function of the membrane and tissue response.

The microporous structure of EZ Cure allows fluids and the nutrients required by the soft tissues to pass through the membrane.

EZ Cure is indicated for Guided Bone Regeneration (GBR) and Guided Tissue Regeneration (GTR) in dental surgery. Guided regeneration enhances the proliferation of osteogenic precursor cells in a defined area.

The regenerative membrane will be fixed to the underlying bone by surgical pins. Three sides of the regenerative membrane will be attached to the jaw, but a fourth side will be left free so that the biomaterial may be introduced into the resulting pocket. Once the biomaterial is in place, the last side of the regenerative membrane will be attached to the bone and sutured in the submucosal plane on the vestibular side if possible.

5.1.5.Antibiotherapy

Start of antibiotherapy the day before the procedure (Amoxicillin 3 g/d orally or Clindamycin 600 mg X 3/d), then treatment continued with Amoxicillin 3 g/d orally or Clindamycin 600 mg X 3/d for 7 days.

5.1.6.Analgesics

Pain relieving treatment with paracetamol 1g X 4 /D. In the event of intense pain, paracetamol 1 g will be replaced with a level II painkiller.

5.1.7.Mouthwash

Mouthwash with Chlorhexidine (Chlorhexidine digluconate at 0.12%) in the hour preceding surgery. The surgical area must be aseptically washed with Chlorhexidine by the surgeon and the patient must perform mouthwashes with Chlorhexidine in the evening after the procedure.

5.1.8.Sutures

The mucoperiosteal flap will be sutured to the vestibular mucosa in 2 planes if possible (submucosal and mucosal) using absorbable monofilament sutures (5/0).

5.2.AUTHORIZED AND UNAUTHORIZED MEDICINES AND TREATMENTS

5.2.1.Authorized treatments

- ✓ Oral antibiotics,
- ✓ Level I, II or III analgesics,
- ✓ Local oral care: mouthwashes, sodium bicarbonate, Xylocaine gel,
- ✓ Antifungal agents.
- ✓ Non-invasive dental care procedures, including in the mandible ~~or maxillary~~ regions close to the implant site. The following procedures are considered as non-invasive: preventive procedures, conservative care, prosthetic care not requiring incisions, dental X-rays and local, non-intraligament anesthesia (Professional agreement) (AFSSAPS recommendation).

5.2.2.Unauthorized treatments

- Mucosal incision in the reconstructed area during the bone healing process.
- Invasive dental care (surgery) in the implanted or directly adjacent areas

- Bisphosphonate treatment.

5.2.3.Emergency treatment

In the reconstructed area

Local infection (isolated local inflammatory signs are not considered to require systemic treatment). Overt infection is defined as a combination of local inflammatory signs (redness and exquisite pain) and a temperature over 38°C or purulent discharge. Treatment may include:

- systemic antibiotherapy with oral or intravenous administration of Amoxicillin and Clavulanic acid, 1g x 3/d or that will be adapted as a function of the results of the bacteriological analyses performed on samples taken from the operated area and on the residual non-implanted hybrid material if required,
- local treatment by washing with saline solution and mouthwashes (see section on authorized treatments),
- should the treatment fail, local debridement by mucosal incision may be required. This must be performed as conservatively as possible so that the infection may be treated without the biomaterial being affected.

Hematoma at the implant site: signs of local accumulation (subcutaneous or submucosal renitent swelling) with cutaneous or mucosal ecchymosis without signs of infection. Treatment consists in local debridement by limited incision allowing the infection to be treated without the biomaterial being affected.

At the BM harvest site

Infection of the harvest site: (isolated local inflammatory signs are not considered to require systemic treatment). Overt infection is defined as a combination of local inflammatory signs (redness and exquisite pain) and a temperature over 38°C or purulent discharge. Treatment may include:

- systemic antibiotherapy with oral or intravenous administration of Amoxicillin and Clavulanic acid, 1g x 3/d,
- local cleansing treatment with saline solution or a local disinfectant,
- should the treatment fail, local debridement by cutaneous incision may be required.

Hematoma of the harvest site: subcutaneous renitent swelling with subcutaneous ecchymosis without signs of infection. Treatment consists in debridement by incision and evacuation of the hematoma.

5.3.METHODS FOR ENSURING THAT THE TREATMENT IS FOLLOWED

NOT APPLICABLE.

5.4.EXPERIMENTAL MEDICINES CIRCUIT

5.4.1.General circuit

MBCP and collagen membrane

BIOMATLANTE (France) will provide each center with:

-10 boxes of 1 syringe containing 5 cc of MBCP + ™

-20 boxes of 1 x 30x40 mm EZ Cure ™ membrane

If required, the devices will be relabeled by BIOMATLANTE or its representative, under the company's responsibility.

Stem cells

The stem cells will be transported from the center participating in the study to the cell production center (round trip) in a refrigerated container (4 °C) by an express courier service in compliance with good cell engineering practices.

5.4.2.Experimental medicines storage conditions

Description of how the product is stored at the pharmacy

MBCP and collagen membrane

The MBCP+™ syringes and the EZ Cure™ membrane must be stored in locked premises, protected from light, at room temperature, and excessive temperatures must be avoided (>50°C). They must not be frozen or quick-frozen or resterilized. If the sterile packaging is damaged, the product must not be used. Furthermore, the investigators or pharmacists will be in charge of the control and accounting of the devices and their dispensation and must use appropriate stock management documents.

At the time the device is placed, the investigator will record the number of the device, its batch number and its date of implantation in the source dossier and in the patient's CRF. After being implanted by the investigator, the utilized devices will be kept for test product control and follow up.

At the end of the trial, the products will all be accounted for by the investigators or pharmacists and the accounting will be validated by the CRA in charge of monitoring the study.

The document used for the control of the final product will be communicated to the supplier on request, for information purposes. The packaging of the utilized devices will be destroyed on-site in accordance with current legislation and good practices and a destruction certificate concerning the devices that have been destroyed will be communicated to the biomaterial supplier on request, for information purposes.

At the end of the study, any unused devices will be returned to the supplier on request, together with a document providing information about the returned devices.

Stem cells

NOT APPLICABLE.

Description of how the product is stored in the department

The same conditions apply as in section 5.4.2.1. (Description how the product is stored at the pharmacy).

Description of how the product is stored at the patients' home

NOT APPLICABLE.

6. STUDY CONDUCT

6.1. STUDY METHODS AND METHODS OF ANALYSIS

6.1.1. Detailed description of the parameters used to assess efficacy

The efficacy and safety of the procedure, the stability of the implant, postoperative pain, bone regeneration and any potential AEs will all be assessed.

6.1.2. Description of the methods and analyses used

Clinical assessments

- Questioning: assessment of postoperative pain, of functional limitations;
- Loco-regional clinical examination:

After the first procedure (bone reconstruction): inspection for any signs of inflammation or of possible infection.

At the time of implant placement: evaluation of the quality of the bone comprising the reconstructed ridge after mucosal incision, assessment of implant stability by palpation.

- Analysis of the preoperative impressions of both dental arches and of the pre- and postoperative photographic images.
- Clinical follow up of implant stability by Resonance Frequency Analysis (RFA) (Osstell)

Radiological assessments

By the clinicians:
- Panoramic X-rays, retroalveolar radiography

By the radiologist:
- CT scan / Cone Beam CT scan:

Qualitative study of the images in 3 planes with a bone window view and parenchymal window setting if required: inspection for any signs of inflammation or local infection, sinusitis or osteitis in the preoperative and early (D7) and late (M9) postoperative periods; qualitative analysis of the newly formed bone in early (D7) and late (M9) postoperative periods.

Quantitative study of the height of the bony ridge to be reconstructed: measurement of the height and width of the ridge in the preoperative and early (D7) and late (M9) postoperative periods of the same cross-section with a bone window view and during reconstruction, in the coronal plane, calculation of reconstructed bone volume and comparison of data in the early (D7) and late (M9) postoperative periods.

Determination of the ideal position and dimensions of the implants in the graft using the scan guide positioned on the patient in the preoperative and early (D7) and late (M9) postoperative periods.

All these data will be used to determine whether or not it will be possible to place an implant in the reconstructed area after the bone healing period and thus answer the principal question of the study: does the experimental bone tissue engineering procedure allow placement of implants in reconstructed areas as forecasted during the initial clinical X-ray assessment and in compliance with good engineering practices?

Subjective evaluations

Discomfort walking
VAS score for pain
Use of painkillers

Biopsy samples histological examination

During the drilling prior to implant placement, a biopsy will be performed and analyzed as follows:
After fixation and decalcification, samples will be prepared for embedding in parrafin.

Each block will be cut. Slices 7 µm-thick will be placed on slides and colored with HES or HPS staining. The tissues and cells of the implant sites and in contact with the bioceramic granules will be analyzed. The amount of mineralized bone tissue, biomaterial and non-mineralized tissue will be determined (Weiss and al, 2007).

Innocuousness of the substitution material

A larger amount of stem cells will be produced than required for reconstruction so that local bacteriological controls can be performed on residual non-implanted hybrid material during the graft (i.e. bone substitute + bone marrow cells). The controls require the seeding of:
- a liquid culture medium for aerobic bacteria with 1 ml of hybrid material mixture (bone substitute + bone marrow cells), followed by 8 days of incubation at 37°C.
- and a liquid culture medium for anaerobic bacteria with 1 ml of hybrid material mixture (bone substitute + bone marrow cells), followed by 8 days of incubation at 37°C.
At the end of the incubation period, each broth will then be systematically sub-cultured on solid medium. If bacteria are detected, they will be identified and the bacterial strains will be kept for 2 years so that, in the event of local infection, the microorganisms responsible the infection will be able to be compared with the microorganisms found in the non-implanted residual hybrid materials (antibiogram and if required, molecular biology analyses).

In the event of complications requiring that the biomaterial be removed, a bacteriological and/or histological analysis may be requested by the surgeon if deemed necessary and compared with the results of the bacteriological analyses performed on the non-implanted residual hybrid materials.

6.2. STUDY CALENDAR

Actions	D-42 (Pre-inclusion visit)	D~~0~~ (Inclusion visit)	D7	M6~~9~~	~~M12~~M9	M2~~76~~ / Study termination
Verification of the selection criteria, information given to the patient and free, informed consent obtained + **Inclusion fax**	X					
Panoramic X-rays	X			X	X	X
Loco-regional clinical examination	X	X	X	X	X	X
History of current treatments, verification of inclusion/exclusion criteria	X					
Impression of both dental arches	X					
Facial and oral cavity photographs	X					X
Retroalveolar radiographs Retroalveolar radiographs or **panoramic X-rays** if the size of the graft is larger than that of a tooth	X	X (Post-graft)		X	X	X
Coagulation assessment	X					
VAS score for pain	X	X	X	X	X	X
Questionnaire on use of painkillers	X	X	X	X	X	X
Bone marrow withdrawal (15 days before the Grafting procedure)	X					
Grafting procedure		X				
Radiological guide, Surgical drill template				X		
CT scan / Cone Beam CT scan	X		X	X		X
Implant placement, biopsy				X		
Clinical follow up of implant stability by Resonance Frequency Analysis (ISQ RFA)				X	X	X
Loading of the implant (prosthesis)					X	
Adverse events, concomitant treatments		X	X	X	X	X

6.3. IDENTIFICATION OF ALL SOURCE DATA NOT IN THE MEDICAL FILE

The following data may be reported directly in the case report forms.
They will not be reported in the source file:
- Verification of the selection criteria
- Concomitant treatment
- Detailed loco-regional examination
- Use of painkillers
- Bone marrow characteristics
- Size and characteristics of the biopsy
- Analysis of the retroalveolar radiographs and of the CT scan / Cone Beam scan
- Adverse events, concomitant treatments

6.4. RULES CONCERNING PATIENT WITHDRAWAL

6.4.1. Criteria for premature study termination

Patients presenting one of the following events:
- Withdrawal of consent,
- Breach of the protocol,
- Graft recovery: if it is necessary to remove the biomaterial (e.g. because of infection) or if migration of the biomaterial is too significant, the hybrid graft must be recovered and the biomaterial removed; after a period of secondary healing, augmentation surgery by grafting of autologous bone or biomaterial must be scheduled (on a case by case basis). In cases where the graft is recovered, it must be kept for histological analysis. The patient is therefore withdrawn from the study after the biopsy.
- Treatment forbidden…

However, patients may only be withdrawn from the study after confirmation by the investigator and the sponsor. In all cases, study termination is permanent.

Not being able to place an implant in M9 (insufficient bone height/width) does not lead to withdrawal from the study. The patient will continue to be followed up until M27 or until he/she presents with a premature discontinuation criterion. The time at which a new scan will be performed must be determined by the practitioner, but the results will all be reported.
Study termination because a patient has not come to the appointments must be investigated. The patients will be contacted twice (in the week following the theoretical date of consultation, then if necessary, in the following week too) before being considered “lost to follow-up”. The investigators must do everything in their power to find patients lost to follow-up and document their state of health. Any patients withdrawn from the study prematurely will be given the best care possible, in compliance with accepted good practice rules.

6.4.2. Procedure for premature withdrawal of patients from the study

When possible and on condition that they accept to, patients withdrawn from the study before M27 will undergo the examinations they would have undergone at the visit in M27 (unless the examinations performed previously were identical to those planned for visit M27 and were performed less than 15 days previously).

Any patients prematurely withdrawn from the study will be replaced.

Patients withdrawn from the study prematurely will be given the best care possible, taking into account the state of their health and their medical history. The care they will receive (modalities and duration of follow-up) has no particular characteristics.
No data concerning a patient withdrawn prematurely from the study will be recorded after the date of withdrawal except for safety data (follow-up of an AE or appearance of an treatment-related AE in the 15 days following the study).

6.4.3. Criteria for discontinuing part of or the entire study (excluding biostatistic considerations)

The study is scheduled to last 39 months: the inclusion period should extend over about 12 months. The study will be terminated at the end of the participation of the last person included, i.e. ~~27~~ 26 months after harvesting of the patient's bone marrow.
The criteria for discontinuing the study are as follows:
- if more than 10 grafts need to be recovered
- the presence of pain not relieved by level III analgesics lasting more than 1 month at the harvest site or the treated region, with a VAS score over 8 in more than 12 patients.

The decision to discontinue the study will affect the entire research project and will be temporary or permanent, depending on the recommendations of a surveillance committee that will be called to meet if one of the above events occur (or at the request of the sponsor or of half of the members of the surveillance committee). The study will be considered terminated only if this is confirmed by the sponsor.
Patients withdrawn from the study prematurely will be given the best care possible, taking into account the state of their health. The care they will receive (modalities and duration of follow-up) has no particular characteristics.
The reasons for permanent or temporary premature discontinuation of the study may also be based on a decision of the Ethics Committee or the AFSSAPS or of the sponsor, for example, if no subjects can be included.
To fill in this section, refer to the "Statistics" section that presents the statistical criteria for discontinuing the study.

7. DATA MANAGEMENT AND STATISTICS

7.1.STUDY DATA COLLECTION AND PROCESSING

7.1.1.DATA COLLECTION

An electronic case report form (CRF) will be created for every patient. All the data required by the protocol must be reported in the CRF. It will include sections on all the steps concerning the follow-up of patients described in the protocol. It must include all the data required to ensure compliance with the protocol and to detect any major deviations from the protocol, and all the data required for the analyses described in the "Statistics" section.

Data will be collected in an electronic CRF that can be accessed at the following address: https://www.dirc-hugo-online.org/csonline/
The electronic CRF will be developed under the responsibility of the Clinical Research Promotion Department of the Nantes University Hospital, who will also be responsible for managing access to the site and for ensuring that it functions properly throughout the study.
The site will be accessed using personal identification numbers and passwords that provide various rights (input, signature, monitoring, etc).
The investigator will be responsible for filling in the CRF. However, the activity may be delegated to a CRA or any other person (defined and identified in the table summarizing the responsibilities that have been delegated in each center) on condition that the source data defined in the paragraph "Identification of all the data to be collected directly in the case report form, that will be considered as source data" be reported at the time they are collected. Any missing data must be reported.

7.1.2.Data codes

By signing the protocol, the principal investigator and all the co-investigators undertakes to keep confidential the identity of the patients participating in the study. At inclusion, the case report form of each patient will be attributed a number including the code for the town in which the patient is seen in consultation (i.e. 3 letters: NAN for Nantes, BER for BERGEN, LIE for Liège and VER for VERONA) and a number indicating the order of inclusion of the patient in the study
Thus, code numbers are attributed as follows:

☐ NAN ☐ BER ☐ LIE ☐ VER

I__I__I
Patient No.

The patient number, the first letters of the patient's surname and first-name and the month and year of birth of the patient (age being a significant data) will be the only information appearing on the CRF that may be used to connect the CRF to the patient à posteriori.
The subjects' anonymity will be guaranteed by reporting the first letter of their surnames and firs-names on all the documents. All nominative data will be deleted.
The case report forms will be dated and signed by the investigator when the patient terminates the study to validate the data.

7.1.3.Data processing

The clinical data will be collected in a data base using data entry forms based on the case report form, in compliance with the protocol and the legislation currently in force.
The structure of the data base and input screens will be approved by the study sponsor.

7.2. STATISTICS

The statistical analysis manager is Dr Bruno GIRAUDEAU
Centre d'Investigation Clinique - Inserm CIC 0202
CHRU de Tours
Bâtiment B2A (4th floor), 2, Bd Tonnellé - 37044 Tours Cedex 9, France
Tel. + 33 (0) 2 47 47 46 18 ; Secretary: + 33 (0) 2 34 37 96 57; Fax: + 33 (0) 2 47 47 46 62
giraudeau@med.univ-tours.fr bruno.giraudeau@univ-tours.fr

7.2.1. Description of the statistical methods, including the calendar of scheduled interim analyses

Variables taken into account

The following variables will be taken into account for the statistical analysis of the principal criterion:

The height and width of the reconstructed ridge, the initial height of the ridge + height of the graft greater than or equal to the length of the prescribed implant (median of the values measured independently by the investigator during the pre-implant consultation, a dental surgeon and a maxillofacial surgeon, and centralized at the end of the study), the initial width of the ridge + the width of the graft greater than or equal to the length of the prescribed implant + 2 mm (median of the values measured independently by the investigator during the pre-implant consultation, a dental surgeon and a maxillofacial surgeon, and centralized at the end of the study), any contraindications viewed in the scan: sinusitis, osteitis.

Signs of inflammation or local or general infection preventing the placement of the implant (excluding other general contraindications), clinical appraisal of the height of the reconstructed bony ridge using a VAS on palpation after incision of the mucosa before placement of the implant, ISQ values, assessment of pain and difficulty in walking (VAS, recording of the number of day(s) the patients experienced pain/difficulty in walking if the VAS >= 1), intensity of the pain, the period of professional inactivity (sick leave, leave without pay), functional limitations, healing times, the use of painkillers, complications related to the study procedure (particularly at the harvest sight and at the receiving site: clinical and radiological examinations), results of the qualitative/quantitative assessment of bone regret,

Statistical analysis

The principal criterion will be assessed for the proportion of patients for whom implant placement is confirmed at ~~9~~ 6 months. The proportion of patients will be estimated selectively and with an accurate confidence interval.

The other variables taken into account for the statistical analysis will be described in terms of frequency and percentage for qualitative variables and in terms of median, minimum and maximum values for quantitative variables.

7.2.2. Statistical rationale for the number of inclusions

The study protocol plans for the inclusion of 40 patients. As this is a pilot study investigating a relatively innovative technique that has never been studied in this indication, it is impossible to justify the number of patients to be included (absence of figures in the literature, absence of personal data). The study is therefore a descriptive study conducted to assess the value and innocuousness in humans of hybrid bone substitutes made up of calcium phosphate ceramics and mesenchymal stem cells and used to reconstruct dental implant sites.

7.2.3.Degree of statistical significance

As the study is a descriptive study, the level of statistical significance has not been determined.

7.2.4.Statistical criteria for discontinuing the study

NOT APPLICABLE (no interim analysis scheduled). Furthermore, the inclusion period (1 year) is too short in terms of the period between inclusion and implant placement (approx. 10 months) to envisage discontinuing inclusions based on the first results.

7.2.5.Method for taking into account missing, unused or invalid data and choice of subjects to be included in the analyses

As this study is a descriptive study, the variables of all the patients will be taken into account on condition that the patient is treated with the hybrid bone graft combining calcium phosphate ceramic scaffold and mesenchymal stem cells

As the study is not a randomized trial, no strategy will be used for the assignment of missing data.

7.2.6.Management of changes made to the plan of analysis of the initial strategy

Any potential changes made to the statistical analysis strategy will be managed by Dr Bruno GIRAUDEAU and will give rise to amendments.

7.2.7.Randomization

NOT APPLICABLE

Rationale:

Context

Five clinical trials are scheduled in the REBORNE project (three in the orthopedic area, and two in the maxillofacial area).

Regarding the design of these trials, the main question concerns whether they should be comparative randomized trials or non-comparative trials.

Issues to be considered

1) On the one hand, some authors, like Chalmers (1975; 1977), consider that randomization has to apply to the very first patient included, mainly because should a non-comparative pilot study demonstrate the apparent unequivocal value of the new procedure, a randomized trial would be hard to plan and would be ethically debatable. Similarly, should the pilot trial demonstrate the apparent worthlessness of the procedure, it would be hard to plan a randomized trial.
2) On the other hand:
   - Some Phase IIA trials are single arm trials (as opposed to phase IIB trials). They allow the collecting of data necessary for the planning of a future comparative study.
   - The procedures we are interested in are non-pharmacological procedures. In such situations, surgeons are “part of the procedure” (Boutron *et al*, 2008). Considering

that the procedures we are interested in are new procedures, we will have to face a learning curve (which is not the case when pharmacological treatments are tested) for both the surgeon and the person in charge of preparing the cells.

- The trial is a multicenter trial: the learning curve impact will apply to each center and only a few patients will be recruited in each center.
- Recruitment: ease of enrolling a patient in a non-comparative trial *versus* a randomized trial in which very different medical approaches are compared (a debatable issue) (Chalmers 1975; Boutron, Moher et al. 2008).

8. PHARMACOVIGILANCE AND MANAGEMENT OF ADVERSE EVENTS

8.1. DEFINITIONS

8.1.1. Adverse events

An adverse event is defined as any harmful event in a patient or clinical trial participant, which is not necessarily related to the study treatment.

Any adverse events observed by the physician or reported by the patient during the study will be noted in the case report form in the appropriate section.

The intensity of the adverse events will be graded according to criteria selected during the drawing up of the protocol (*provide the list of evaluation criteria in the appendix*). Any adverse events not appearing in the selected classification will be graded as follows:

1 = benign
2 = moderate
3 = severe
4 = life-threatening

8.1.2. Adverse effects

An adverse effect is suspected in all cases where an adverse event is found to have a causal relationship, irrespective of its significance (doubtful, plausible, possible, certain), with the study treatment or the comparator or the protocol.

8.1.3. Serious adverse events or effects

An adverse effect is considered serious if it:

* results in death,
* is life-threatening,
* results in temporary or permanent handicap or incapacitation,
* requires or prolongs patient hospitalization,
* results in an abnormality or birth defect,
* is a serious medicinal reaction (i.e. requires management to prevent deterioration of the patients' condition to one of the above states).

8.1.4. Expected adverse events or effects

An expected adverse event (EAEv) is one that is mentioned in the most recent version of the Investigator's Brochure or in the most recent user guide of the CE-marked Medical Device (MD).

The reporting of expected serious adverse events or effects by the sponsor to the competent authorities may be deferred.
The serious adverse events that can be expected with this protocol are as follows:
Concerning the study medication
No serious adverse event expected
Concerning the protocol
- Allergy related to one to the constituents of the anesthesia,
- Local infection not curbed by systemic antibiotherapy, more or less associated with simple surgical debridement,
- Trocar needle rupture

Concerning the disorder
No serious adverse event expected

8.1.5. Unexpected adverse effects

An unexpected adverse effect (UAEs) is any effect whose nature, severity, frequency or outcome is not consistent with the information concerning the products, procedures and methods used during the study as defined in the Investigator's Brochure the Summary of Product Characteristics or the user guide.
The sponsor must notify the competent authorities of the unexpected serious adverse effect in the 7 to 15 days following the reporting of the effect to the sponsor.
Every quarter, the sponsor will send a summary table of all the USAEs observed to the Ethics Committee and the study investigators.
The only unexpected serious adverse effect envisaged is a positive result obtained following bacteriological analysis of the non-implanted residual hybrid material (bone substitute and bone marrow). The event would have to be declared to the sponsor (within 24h).

8.2. SAFETY EVALUATION CRITERIA (if applicable)

8.2.1. Special safety-related evaluation criteria

8.2.2. Methods used and schedule for measuring, collecting and analyzing safety parameters

Actions	D-42 (Pre-inclusion visit)	D0 (Inclusion visit)	M9	M12	M27 / Study termination
Panoramic X-rays	X		X	X	X
Loco-regional clinical examination	X	X	X	X	X
Photo of both dental arches AND of the graft region	X		X		X
Retroalveolar radiographs			X	X	X
VAS score for pain		X	X	X	X
CT scan / Cone Beam CT scan	X		X		X
Grafting procedure		X			
Implant placement, biopsy			X		
Clinical follow up of implant stability by Resonance Frequency Analysis (ISQ RFA)			X	X	X
Loading of the implant (prosthesis)				X	
Adverse events, concomitant treatments		X	X	X	X

The safety assessment criteria will be evaluated and collected by the investigators throughout the study and reported to the sponsor during monitoring visits. They will include symptoms, dates, outcomes, measures taken, and if required, examination and laboratory test results. Once they have been analyzed by the sponsor, the data will be summarized and if necessary, information reported back to the investigators.
The results of the bacteriological analyses performed on the non-implanted residual hybrid material will be communicated at M1 at the latest.
The safety criteria selected are microbial non-contamination, cell viability, the presence of precursor cells (CFU-F) and the absence of culture transformation criteria (karyotype and FISH normality, and hTERT negativity).

8.3.LIST OF EXPECTED ADVERSE EVENTS

The adverse events that can be expected with this protocol are as follows:
Concerning the medical device and the production of cells harvested from bone marrow:
Genetic modification of the cells
Phenotypic modification of the cells
Allergy to one of the cell culture products
Presence of microorganisms in the treated cell culture

Concerning the protocol:
Physical risks associated with the bone marrow harvest site (posterior superior iliac spine)

Local bleeding: a compressive dressing may be required
Local infection at the harvest site
Residual pain after 48 h: generally regresses with analgesics such as paracetamol, burning sensation
Difficulty walking for 48 h
Trocar needle rupture
Persistent pain and inflammation at the harvest site (> or = 7 days with treatment)
Postoperative bleeding (< or = 1 day) at the harvest site
Harvest site infection
Temporary functional lameness of the leg
Harvest site hematoma

Physical risks associated with the receiving site

Exposure / infection / elimination of the graft: possible, not very painful, serious because the graft will be suspected, but not very serious for the patient (the material is not toxic for the conjunctiva around the bone), temporarily physically restrictive because another procedure would most certainly be required to remove the biomaterial, resulting in premature withdrawal of the patient from the study

Inflammation for several weeks (notably related to the onlay membrane)

Superficial gingival infection potentially aggravated by the onlay membrane

Migration of the biomaterial along the length of the alveolar bone on both sides of the reconstructed area

Persistent pain and inflammation (more than 3 weeks) at the implant site requiring increased doses of analgesics compared to normal requirements

(1) Postoperative edema (> or = 7 days under treatment)

(1) Postoperative bleeding (> or = 1 day)

Local infection at the implant site

Healing disorders (mucosal disunion)

Graft exposure

Graft resorption

Graft resorption with loss of the graft

Concerning the disorder:
Local infection,
General infection,

The document used as a reference to determine the expected nature of the events must be identified and its reference noted (with date and version No.).

8.4.MANAGEMENT OF ADVERSE EVENTS

8.4.1.Reporting of SAEs

Any SAE whether expected or unexpected (except those specified in the preceding section) must be reported by means of a SAE report form. The investigator must check that the information provided in the form is accurate and clear (no abbreviations used, etc.).
The SAE must be immediately reported to the sponsor (within 24 hours of being observed by the investigator) by fax (Clinical Research Promotion Department of the Nantes University Hospital, fax:+ 33 (0) 2 53 48 28 36).
Once the sponsor has received a SAE report, the event must be declared to the competent authorities. An annual safety report is established once a year.

8.4.2.Independant Surveillance Committee

The Independant Surveillance Committee (ISC) is an advisory committee responsible for advising the study sponsor and trial coordinator/principal investigator on the safety of the clinical trial. Its members, competent in the field of clinical trials (pathology and methodology) are not involved in the study. They are nominated for the duration of the study and undertake to respect the study's requirements, by not divulging confidential information, for example. The members of the ISC are selected collegially by the trial coordinator/principal investigator and the sponsor. The ISC receives the annual safety reports and its opinion may be requested by pharmacovigilance if a SUSAR or SAE is difficult to analyze or if a doubt on the benefit/risk ratio arises during the study.
The list of ISC members is provided in Appendix 6.

8.5.MODALITIES AND DURATION OF FOLLOW-UP OF SUBJECTS AFTER THE ONSET OF AN ADVERSE EVENT

Adverse events and SAEs will be collected by questioning the patient (about the period starting at the time the informed consent form is signed by the patient until the end of the patient's follow-up in the study, about any concomitant treatments taken since the previous visit, about any new events having occurred in his/her state of health or quality of life).
The adverse events will be followed-up by the investigator until they have stabilized or resolved, or until the patient terminates the study. The SAEs will be followed by the investigator until they have stabilized or resolved.
The anonymous results of the examinations and analyses performed in the framework of the management of the AEs or SAEs will be communicated to the sponsor if requested.

9. ADMINISTRATIVE AND REGULATORY ASPECTS

9.1. RIGHT OF ACCESS TO SOURCE DATA AND DOCUMENTS

The medical data concerning the patients will only be communicated to the sponsor or to persons duly authorized by the sponsor and if necessary, to the competent health authorities under conditions that guarantee they remain confidential.
The sponsor and regulatory authorities may request direct access to the medical files to check the clinical trial procedures and/or data, without breaching the confidentiality of the documents and in the limits authorized by the law and regulations.
The data collected during the trial may be processed by computer in compliance with the requirements of the CNIL (compliance with the reference method MR001).

9.2. MONITORING OF THE TRIAL

The trial will be monitored by the Clinical Research Promotion Department. A Clinical Research Associate (CRA) will visit each site on a regular basis to verify the quality of the data reported in the case report forms.

The protocol has been classified based on the level of risk it represents for the patient taking part in the research project. It falls into one of the following category : risk B: foreseeable risk similar to that of usual care

The on-site monitoring visits will be organized by making an appointment with the investigator. The CRAs must be able to consult:
- the case report forms used to collect the data concerning the patients included in the study,
- the medical and nursing files of the patients,
- the investigator file.

9.3. INSPECTION / AUDIT

An inspection or audit may be performed in the framework of the study.

9.4. ETHICAL CONSIDERATIONS

9.4.1. Written informed consent

The investigator undertakes to provide patients with clear and accurate information about the protocol and to obtain their written informed consent (patient information document and informed consent form provided in appendix). The investigator will give the patients a copy of the patient information document and the informed consent form. Patients may only be included in the study after they have become familiar with the information document and after they have signed and dated the informed consent form. The investigator must also sign and date the informed consent form. At least 2 copies of the two documents will be printed out on paper so that both the patient and the investigator may have a copy. The original investigator's document will be kept in the investigator's file.

9.4.2. Ethics Committee

The sponsor undertakes to submit the study project for prior authorization to an Ethics Committee (EC). The information communicated to the committee concern the modalities and nature of the research and the guarantees for the patients participating in the trial.

9.5. PROTOCOL AMENDMENTS

Any requests for major changes will be sent by the sponsor for authorization or an opinion to the AFSSAPS and/or the relevant Ethics Committee in compliance with Law No. 2004-806 dated 9 August 2004 and its application orders.

The amendments will give rise to an updated version of the protocol that must be dated.
The patient information documents and the informed consent forms will also be amended if required.

9.6. SUBMISSION TO THE COMPETENT AUTHORITIES

The protocol has been submitted to the AFSSAPS for authorization.

9.7. FILE CONCERNING PERSONS TAKING PART IN BIOMEDICAL RESEARCH

NOT APPLICABLE.

9.8. FINANCING AND INSURANCE

The sponsor will finance the study and in compliance with regulations, will take out legal liability insurance coverage guaranteeing that patients will be indemnified if necessary.

9.9. RULES PERTAINING TO PUBLICATION

A copy of the publication will be provided to the Nantes University Hospital, i.e. the study sponsor, who will necessarily be cited. The authors will be determined as a prorata of the patients included. The trial coordinator will draw up the list of authors.
No restrictions will apply to the public communication of the results (AFSSAPS base).

9.10. FATE OF THE BIOLOGICAL SAMPLES

Not applicable

LIST OF APPENDICES

! The appendices must be paginated individually!

1. *List of investigators (identity, function, specialty, place of exercise = institution & department, ADELI number (official practitioner registration number), full address and contact details)*
2. *Bibliographic references*
3. *Patient information document*
4. *Bone marrow harvesting procedure*
5. *Pre-implant surgical procedure*
6. *List of principal participants and contact details (Scientific Committee, CRO, Analytical Laboratories, Major suppliers, etc…)*
7. *Case report form / data collection form / questionnaires/ pre-filled SAE report*
8. *Notice d utilisation de EZ-Cure+ ™*
9. *Notice d utilisation de Frios ®*

APPENDIX 1: LIST OF INVESTIGATORS

Note: the appended list of investigators must include the full contact details of the institution and the department where the investigator works (address, telephone, fax, email), as well as the ADELI number of each investigator.

	PRIMARY CONTACT	OTHER CONTACT
Dental Medical Department C.H.U. Domaine Universitaire du Sart Tilman Bâtiment B 35 4000 LIEGE 1 ***BELGIUM*** Phone: +32 4 366 82 90 / + 32 4 270 31 23 - Fax: +32 4 366 82 89 http://www.chuliege.be/lieux/sart.html	*Professeur Eric ROMPEN* Phone:+32 4 366 82 90 - Fax:+4 366 82 89 eric.rompen@chu.ulg.ac.be	Geoffrey LECLOUX: geoffrey_lecloux@hotmail.com
Oral and Maxillofacial Surgical Department NANTES UNIVERSITY HOSPITAL - Hôtel-Dieu 1 place Alexis-Ricordeau 44093 - Nantes Cedex 1 ***FRANCE*** Tel. + 33 2 40 08 36 79 - Fax + 33 2 40 08 36 68	*Professeur Jacques-Marie MERCIER* *Assistant: Christine Puget - Christine.Puget@chu-nantes.fr - 83 699* Secretary: Genevieve Bertrand - genevieve.bertrand@chu-nantes.fr - 83669	*Dr CORRE Pierre (REBORNE - WP6 leader)* pierrecorre@hotmail.com, pierre.corre@chu-nantes.fr Dr HUET Pascal 3 r Béraudière 44000 NANTES Direct tel. 06 19 96 19 95 Tel. + 33 2 51 86 86 75 - fax: + 33 2 51 86 86 76 phuet001@cegetel.rss.fr Dr PERRIN jean-philippe jeanphilippe.perrin@chu-nantes.fr ---------- **DENTAL CARE CENTER (ODONTOLOGY)** NANTES UNIVERSITY HOSPITAL - Hôtel-Dieu

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Dentistry and Maxillo-Facial Department University of Verona Piazzale L. A. Scuro, 10 37134 Verona ***ITALY*** Phone: - , Fax: - http://www.medicina.univr.it/fol/main	http://www.medicina.univr.it/fol/main?ent=persona&id=1021#AreeRicerca *Professor Pier Francesco NOCINI* Phone: + 39 0 45 812 42 51 - Fax: + 39 0 45 8027437 Pierfrancesco.nocini@univr.it INCLUDEPICTURE "http://www.medicina.univr.it/fol/image/null.gif" * MERGEFORMATINET	Pr Daniele DESANTIS Phone: + 39 0 45 812 4097 daniele.desantis@univr.it Dr. Andrea Frustaci Andreas.frustaci@univr.it Dr. Antonio de Gemmis Antonio.gemmis@univr.it
Department of Clinical Dentistry Faculty of Medicine and Dentistry University of Bergen Årstadvn. 17 Postboks 7804 5020 BERGEN ***NORWAY*** Phone: +47 55 58 65 60 - Fax: +47 55 58 65 77 http://www.uib.no/iko/en	*Professor Kristina ARVIDSON* Phone: +47 55 58 66 41 Kristina.arvidson@iko.uib.no Dear Veronique, Please use my last email address Kristina.arvidson@iko.uib.no	Prof Sølve HELLEM Phone: +47 55 58 66 55 Solve.Hellem@iko.uib.no ---------- Prof Kamal MUSTAFA Phone: +47 55 58 60 97 Kamal.mustafa@iko.uib.no

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APPENDIX 2: BIBLIOGRAPHIC REFERENCES

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Appendix 4: Protocol for harvesting bone marrow for the culture of medullary precursor cells

(Adapted from the guide of Bone Marrow Aspiration Good Practices, the French Hematology Society (SFH), the French Cell Hematology Group (CFHC), the Hospital Hematology Board (CHH), the French National Union for Hospital Biologists (SNBH), June 2003)

General points

Before the procedure the practitioner must ensure that:
- the patient does not suffer from any serious coagulation disorders that could require substitution therapy,
- the patient is receiving VKA therapy, which should be adjusted if necessary so that the INR does not exceed 2.5
- the patient does not have a history of allergy to iodine or to local anesthetics, or a history of hematoma, or hemorrhage
- the patient has not received localized radiotherapy contraindicating withdrawal from the irradiated site
- the patient has no major skin lesions or diseases.

The sample will be taken by a clinician (maxillofacial surgeon, prosthetist-orthotist, or by a biology specialist physician or pharmacist with the required qualifications and legal competence.

Medullary aspiration will be performed in a surgical environment to guarantee the sterility of the sample and so that the patient may be taken care of rapidly in the event of a problem.

The patient will be informed of the nature of the procedure and any possible complications by the prescribing physician and will be prepared for the sample withdrawal. Anxious patients may be treated with benzodiazepines 30 minutes before the procedure (e.g. sublingual administration of Alprazolam 0.25 mg). The patient will be proposed an inhaled analgesic such as an equimolecular mixture of oxygen and nitrous oxide (Entonox or Kalinox).

Materiel

1. Miscellaneous
- an aspiration tray
- a sterile field
- a non-sterile field
- sterile gloves
- sterile compresses
- a 10 ml sterile Luer lock syringe and a needle for subcutaneous administration (orange) of local anesthetic
- compressive dressing (Méfix™, Elastoplast™...)
- a prescription for the examination and a set of patient labels
- a container for used needles
- a garbage bag for incineration

2. Skin disinfection material
- Betadine Scrub™ for cleaning the skin
- Sterile saline solution in 20 ml ampoules
- Betadine™ for disinfecting the skin

3. Anesthetic products
- EMLA™ (lidocaine and prilocaine)

- Adrenalized Xylocaine at 1 % (lidocaine hydrochloride + epinephrine)

4. Material for aspiration and smearing the sample

- Trocar-tip (e.g. Mallarmé or equivalent) fitted with stylets of varying diameters and lengths
- a 20 ml sterile Luer lock syringe for sample aspiration with a sterile stopper
- clean, fat-free ground-glass slides with a frosted area for patient identification
- a slide holder for transportation.

Identification of the site of withdrawal

The patient must lie in the ventral decubitus position. The operator identifies the iliac spine by bilateral location following the iliac crest from the front to the back.

Analgesia and antisepsis

1. Application of an EMLA™ patch on the site of withdrawal, 1.5 to 4 hours before the procedure. The time of application will be written directly on the dressing. The anesthetizing cream will be removed with a dry compress.
2. Inhaled analgesia with an equimolecular mixture of oxygen and nitrous oxide (Entonox™ or Kalinox™).
3. Disinfection in compliance with the “invasive procedure” protocol.
   a. Antiseptic washing of hands of the operator and the state registered nurse (hygiene protocol)
   b. Wearing of sterile gloves
   c. Cleaning of the area with Betadine Scrub™ (in the event of allergies, choose and alternative with the pharmacy)
   d. Rinsing with sterile compresses soaked with sterile water, from the center to the periphery of the site
   e. Drying with sterile compresses
   f. Application of Betadine™ for skin disinfection from the center to the periphery of the site
   g. Respect the drying time (2 to 3 min)
   h. Placement of the sterile barrier

4. Local anesthesia of the various planes using adrenalized Xylocaine at 1 %, without exceeding a volume of 5 ml. Wait for the anesthetic to take effect (approx. 5 min).

Injection and smearing of the sample

1. Puncture with the trocar needle

   a. Check the mobility of the stylet in the trocar and if required, adjust the depth stop as a function of the patient’s build.
   b. Work through the soft tissue to reach the bone. Exert controlled pressure perpendicularly to the external table of the bone until the cortical area is reached, rotating the trocar depending on the hardness of the bone. In the iliac spine, the progression is stopped by the trocar becoming implanted in the bone.
   c. Withdraw the stylet. The operator’s helper provides a previously purged 20 ml sterile syringe that should be rapidly placed on the trocar or needle.
   d. Aspirate until a few ml of medullary fluid become visible (a few ml only so the sample is not hemodiluted), then make a quarter turn with the syringe and aspirate the BM[1].
   e. Drive the trocar in a few mm and repeat the operation.
   f. Check the quality of the medullary blood by placing a drop of the sample (spots) on 3 slightly inclined slides. Screw a sterile cap on the syringe and shake it with slow rotational movements to prevent the sample from coagulating.

[1] La phrase qui suit est incomplète dans la version française. Je ne peux donc pas proposer de traduction

g. Replace the stylet and remove the trocar along the axis of penetration and dispose of them in the used needle container.

h. Rapidly prepare 5 to 10 homogeneous smears using the decanted spots.

i. Apply pressure to the injection site with sterile compresses for a relatively long period given the risk of hemorrhage. Remove the compresses and clean the injection site with an iodinated product and dress the site with a compressive dressing if required.

2. Packaging of the BM

The sample will be preserved on dry heparin, placed in a refrigerated container shipped immediately by special transport to one of the local laboratories participating in the study in compliance with the partnership agreements.

3. Preparation of the smears [3]

Separate the medullary fluid and the blood by placing a few drops of sample from the syringe on 3 slides that have been previously slightly inclined, then prepare the smears in the non-sterile field using the crushing technique.

Width the end of a slide, remove a “lump” of medullary fluid and place it on the upper third of the slide. Take a clean slide and slide it in parallel movement over the first, without applying too much pressure, until reaching the extremity of the slide. Five to 10 slides must be prepared in this manner.

The slides are then air dried with no ventilation or shaking, identified at the patient’s bedside and then sent to the laboratory in an envelope, together with a prescription and the patient’s clinical-biological form and labels.

Monitoring of the patient

The patient must be allowed to rest while and his/her dressing is monitored for about 15 minutes.

The patient may resume normal activities in the hour following the withdrawal of the sample.

In most cases, no particular further monitoring is required by healthcare personnel. The dressing may be removed by the patient a few hours after the procedure.

The included patients will have their bone marrow sampled as follows: for each included patient, a 15 ml sample of bone marrow will be removed from the iliac crest after local anesthesia and sedation. The sample will be withdrawn by an experienced hematologist in the Cardiology Department. The sample will be withdrawn in the room where coronarographies are performed. The patient will be made to lie in the ventral decubitus position and will be given an intravenous injection of Morphine (0.1 mg/kg) before being anesthetized locally by subcutaneous injection of Xylocaine at 2%. Two hours before the procedure, the patient will be administered an intravenous injection of 1 g of PERFALGAN and 100 mg of ATARAX. The posterior iliac spine will be punctured in 2 to 3 places through a skin puncture using a Gallini trocar needle. Two 5 ml fractions of bone marrow will be collected in two syringes on dry heparin. The bone marrow will then be transferred to a pouch containing ACD anticoagulant (MacoPharma). The risk of hematoma at the injection site will be minimized by the application of manual pressure for 20 minutes and a compressive dressing for 48 hours with clinical monitoring. The bone marrow sample is then dispatched at room temperature by a certified carrier and packaged in the corresponding French Blood Institute.

Attachment 3: Official documents justifying the modification of partner #17 UNIVR

UNIVERSITÀ DEGLI STUDI DI VERONA

AREA AFFARI GENERALI E LEGALI

BC/ep

Decreto n. 490
del 17/02/2010
Prot. n. 9932
Tit. VI/3

IL RETTORE

VISTO lo Statuto dell'Università degli Studi di Verona emanato con Decreto Rettorale 7 ottobre 1994 n. 6435, modificato con Decreto Rettorale 23 giugno 2000 n. 11448, con Decreto Rettorale 8 gennaio 2002 n. 2 e, da ultimo, con Decreto Rettorale 25 agosto 2005 n. 1624;

VISTE le disposizioni del D.P.R. 11 luglio 1980 n. 382 in materia di Dipartimenti;

VISTO il Regolamento Generale d'Ateneo, Parte I, emanato con Decreto Rettorale 25 settembre 1997 n. 8999, ed in particolare il titolo X *"Dipartimenti"*;

VISTA la deliberazione del Senato Accademico in composizione allargata del 22 dicembre 2009, di approvazione della manovra di riorganizzazione dipartimentale e, in particolare, di individuazione di quindici nuovi Dipartimenti, aggregati per omogeneità tematica e per obiettivi di ricerca strategici, nonché secondo i principali SSD di riferimento;

VISTO il *"Regolamento Quadro di funzionamento dei Dipartimenti"* approvato dal Senato Accademico in composizione allargata del 22 dicembre 2009 ed emanato con Decreto Rettorale n. 131 del 14 gennaio 2010;

VISTE le opzioni di afferenza ai costituendi Dipartimenti trasmesse dal personale docente e ricercatore;

TENUTO CONTO che il Senato Accademico in composizione allargata, nella seduta del 16 febbraio 2010, ha definitivamente approvato la manovra di riassetto dipartimentale stabilendo, in particolare:

- l'individuazione dei quindici nuovi Dipartimenti, aggregati per omogeneità tematica e per obiettivi di ricerca strategici, nonché secondo i principali SSD di riferimento;
- l'elenco dettagliato del personale docente e ricercatore afferente presso ciascuno dei costituendi Dipartimenti;
- le linee guida per la costituzione delle dotazioni organiche di personale amministrativo-contabile dipartimentale;
- l'avvio delle procedure elettive per la scelta dei 15 Direttori di Dipartimento, dando mandato al Rettore di emanare il decreto istitutivo;

DECRETA

ART. 1
Istituzione

A decorrere dal 17 febbraio 2010, sono istituiti i seguenti Dipartimenti:
- Dipartimento di Arte, Archeologia, Storia e Società;
- Dipartimento di Biotecnologie;
- Dipartimento di Chirurgia;
- Dipartimento di Economia Aziendale;
- Dipartimento di Filologia, Letteratura e Linguistica;
- Dipartimento di Filosofia, Pedagogia e Psicologia;
- Dipartimento di Informatica;
- Dipartimento di Lingue e Letterature Straniere;
- Dipartimento di Medicina;
- Dipartimento di Patologia e Diagnostica;
- Dipartimento di Sanità Pubblica e Medicina di Comunità;
- Dipartimento di Scienze della Vita e della Riproduzione;
- Dipartimento di Scienze Economiche;
- Dipartimento di Scienze Giuridiche;
- Dipartimento di Scienze Neurologiche, Neuropsicologiche, Morfologiche e Motorie.

ART. 2
Progetto, attività di ricerca e settori scientifico disciplinari

Il progetto, l'attività di ricerca ed i settori scientifico disciplinari dei Dipartimenti di cui all'art. 1 sono specificamente indicati nella scheda allegata al presente Decreto sotto la lettera A).

ART. 3
Personale docente e ricercatore

Ai Dipartimenti di cui all'art. 1, afferiscono i docenti ed i ricercatori specificamente indicati nella scheda allegata al presente Decreto sotto la lettera B).

ART. 4
Attivazione dei Dipartimenti

L'attivazione dei Dipartimenti di cui all'art. 1 avverrà con successivo Decreto Rettorale, a seguito della approvazione da parte del Consiglio di Amministrazione della assegnazione ai nuovi Dipartimenti delle risorse finanziarie, delle attrezzature, degli spazi, del personale tecnico-amministrativo, nonché della individuazione dei Segretari Amministrativi.

IL RETTORE
(Prof. Alessandro Mazzucco)

ALLEGATO A)

INDICE

Dipartimento
ARTE, ARCHEOLOGIA, STORIA E SOCIETÀ
(ARTS, ARCHAEOLOGY, HISTORY, AND SOCIETY)

1. Il Progetto

Il Dipartimento promuove e coordina l'attività di ricerca scientifica, teorica e applicata, tanto dal punto di vista descrittivo quanto dal punto di vista storico, nelle aree di ricerca che comprendono lo studio dell'ambiente fisico e antropizzato; dell'antropologia culturale, della storia delle religioni, delle scienze sociali; della storia (antica, medievale, moderna e contemporanea); della teoria della critica d'arte, del restauro e della museologia; della storia dell'arte antica, medievale, moderna e contemporanea; dell'archeologia.

Il Dipartimento

- favorisce lo sviluppo di rapporti di collaborazione e scambio di docenti e studenti con altre Università sia nazionali sia internazionali;
- divulga i risultati della ricerca nel rispetto della libertà e dell'autonomia di ricerca e d'insegnamento di ogni singolo docente/ricercatore, cui sono riconosciuti pari dignità e il diritto di accedere ai finanziamenti per la ricerca;
- incoraggia e sostiene la partecipazione a progetti di ricerca nazionali e internazionali relativi alle tematiche caratterizzanti l'attività scientifica del Dipartimento.

2. In ragione di ciò le attività di ricerca che si svolgono all'interno del Dipartimento si focalizzano:

(a) sugli ambienti e le risorse della superficie terrestre, nonché sui modi con i quali, nelle proprie trasformazioni, si integrano costituendo unità geostoriche rilevanti dal punto di vista territoriale, paesaggistico, urbanistico;

(b) sulla cultura e sulle culture, le ibridazioni culturali, la storia delle religioni;

(c) sulla storia: antica (tanto delle aree del Mediterraneo, quanto del Vicino Oriente), medievale, moderna e contemporanea; sulla storia delle culture e delle civiltà che si fondano sul libro e sul documento; su produzione, ordinamento, diffusione, conservazione, gestione e uso dei materiali archivistici e librari, su qualsiasi supporto;

(d) sulle diverse società in una prospettiva diacronica compresa tra la preistoria e la contemporaneità, a partire dalle tracce materiali individuabili, di origine sia antropica che naturale;

(e) sulla storia dell'architettura e delle arti visive tra medioevo ed età contemporanea; sulla didattica della disciplina; sulla letteratura artistica, la critica d'arte e la storiografia artistica; sull'organizzazione dei musei; sulla storia delle tecniche artistiche; sulla conservazione e il restauro;

(f) sullo studio concernente la storia dei rapporti fra gli attori statuali e non statuali del sistema internazionale;

(g) sulla teoria, la storia e la metodologia della ricerca sociale, articolandosi in varie aree che vanno dalla sociologia in generale, alla metodologia e tecnica della ricerca sociale, alla progettazione e valutazione degli interventi di servizio sociale, alla storia della sociologia;

(h) sulla lettura sociologica dei fenomeni della cultura, da quelli assiologici a quelli comunicativi e della socializzazione e formazione (anche delle risorse umane), fino all'impatto sociale dei mass media e delle tecnologie avanzate.

(i) sugli studi relativi al rapporto fra la società e il mondo della produzione dei beni, dell'industria e del lavoro, a partire dalle relazioni industriali fino all'impatto sociale dell'economia e delle trasformazioni dovute alla produzione e alla distribuzione della ricchezza; sull'analisi del rapporto ambiente-società a livello sociologico, tanto dal punto di vista dei sistemi sociali urbani, quanto dal punto di vista delle comunità locali e dei sistemi sociali rurali.

3. **I SSD di riferimento**, ai quali si fa riferimento per ogni ulteriore definizione, sono i seguenti:

AREA 08 – INGEGNERIA CIVILE E ARCHITETTURA		
SSD approvati CUN 4.11.2009		*SSD attuali*
Macrosettore - Codice e denominazione	*SSD - Codice e denominazione*	
08/E DISEGNO, STORIA, RESTAURO	**08/E2 : STORIA DELL'ARCHITETTURA**	ICAR/18 STORIA DELL'ARCHITETTURA
AREA 10 – SCIENZE DELL'ANTICHITÀ, FILOLOGICO-LETTERARIE E STORICO-ARTISTICHE		
SSD approvati CUN 4.11.2009		*SSD attuali*
Macrosettore - Codice e denominazione	*SSD - Codice e denominazione*	
10/A SCIENZE ARCHEOLOGICHE	**10/A1 : ARCHEOLOGIA**	L-ANT/01 PREISTORIA E PROTOSTORIA L-ANT/04 NUMISMATICA L-ANT/06 ETRUSCOLOGIA E ANTICHITÀ ITALICHE L-ANT/07 ARCHEOLOGIA CLASSICA L-ANT/08 ARCHEOLOGIA CRISTIANA E MEDIEVALE L-ANT/09 TOPOGRAFIA ANTICA L-ANT/10 METODOLOGIE DELLA RICERCA ARCHEOLOGICA
10/B STORIA DELL'ARTE	**10/B1 : STORIA DELL'ARTE**	L-ART/01 STORIA DELL'ARTE MEDIEVALE L-ART/02 STORIA DELL'ARTE MODERNA L-ART/03 STORIA DELL'ARTE CONTEMPORANEA L-ART/04 MUSEOLOGIA E CRITICA ART. E DEL RESTAURO
10/D SCIENZE DELL'ANTICHITÀ	**10/D1 : STORIA ANTICA**	L-ANT/02 STORIA GRECA L-ANT/03 STORIA ROMANA
19/N CIVILTÀ DELL'ORIENTE	**10/N1 : CIVILTÀ DELL'ORIENTE ANTICO**	L-OR/01 STORIA DEL VICINO ORIENTE ANTICO L-OR/02 EGITTOLOGIA E CIVILTÀ COPTA L-OR/03 ASSIRIOLOGIA L-OR/04 ANATOLISTICA L-OR/05 ARCH. E ST. DELL'ARTE DEL VICINO ORIENTE ANT. L-OR/06 ARCHEOLOGIA FENICIO-PUNICA L-OR/07 SEMITISTICA - LINGUE E LETT. DELL'ETIOPIA L-OR/08 EBRAICO
AREA 11 – DELLE SCIENZE STORICHE, FILOSOFICHE, PEDAGOCICHE, PSICOLOGICHE E STORICO-ARTISTICHE		
SSD approvati CUN 4.11.2009		*SSD attuali*
Macrosettore - Codice e denominazione	*SSD - Codice e denominazione*	
11/A STORIA	**11/A1 : STORIA MEDIEVALE**	M-STO/01 STORIA MEDIEVALE
	11/A2 : STORIA MODERNA	M-STO/02 STORIA MODERNA M-STO/03 STORIA DELL'EUROPA ORIENTALE
	11/A3 : STORIA CONTEMPORANEA	M-STO/04 STORIA CONTEMPORANEA
11/B SCIENZE DEL LIBRO, DELLE RELIGIONI E DEMOETNOANTROPOLOGICHE	**11/B1 : SCIENZE DEL LIBRO, DEL DOCUMENTO E STUDI STORICI SUL CRISTIANESIMO**	M-STO/07 STORIA DEL CRISTIANESIMO E DELLE CHIESE M-STO/08 ARCHIVISTICA, BIBLIOGR., BIBLIOTECONOMIA M-STO709 PALEOGRAFIA
	11/B2 : SCIENZE DEMOETNOANTRO-POLOGICHE E STORICO-RELIGIOSE	M-DEA/ 01 DISC. DEMOETNOANTROPOLOGICHE M-STO/06 STORIA DELLE RELIGIONI
11/C GEOGRAFIA	**11/C1 : GEOGRAFIA**	M-GGR/01 GEOGRAFIA M-GGR/02 GEOGRAFIA ECONOMICO POLITICA
AREA 14 – SCIENZE POLITICHE E SOCIALI		
SSD approvati CUN 4.11.2009		*SSD attuali*
Macrosettore - Codice e denominazione	*SSD - Codice e denominazione*	
14/B STORIA POLITICA	**14/B1 : STORIA DELLE DOTTRINE E DELLE ISTITUZIONI POLITICHE**	SPS/02 STORIA DELLE DOTTRINE POLITICHE SPS/03 STORIA DELLE ISTITUZIONI POLITICHE
	14/B2 : STORIA DELLE RELAZIONI INTERNAZIONALI, DELLE SOCIETÀ E DELLE ISTITUZIONI EXTRAEUR.	SPS/05 STORIA E ISTITUZIONI DELLE AMERICHE SPS/06 STORIA DELLE RELAZIONI INTERNAZIONALI SPS/13 STORIA E ISTITUZIONI DELL'AFRICA SPS/14 STORIA E ISTITUZIONI DELL'ASIA

14/C SOCIOLOGIA	**14/C1 : SOCIOLOGIA GENERALE, GIURIDICA E POLITICA**	SPS/07 SOCIOLOGIA GENERALE SPS/11 SOCIOLOGIA DEI FENOMENI POLITICI SPS/12 SOCIOLOGIA GIURIDICA, DELLA DEVIANZA E MUTAMENTO SOCIALE
	14/C2 : SOCIOLOGIA DEI PROCESSI CULTURALI E COMUNICATIVI	SPS/08 SOCIOLOGIA DEI PROCESSI CULTURALI E COMUNICATIVI
	14/D1 : SOCIOLOGIA DEI PROCESSI ECONOMICI, DEL LAVORO, DELL'AMBIENTE E DEL TERRITORIO	SPS/09 SOCIOLOGIA DEI PROCESSI ECONOMICI E DEL LAVORO SPS/10 SOCIOLOGIA DELL'AMBIENTE E DEL TERRITORIO

Dipartimento
FILOLOGIA, LETTERATURA E LINGUISTICA
(PHILOLOGY, LITERATURE, AND LINGUISTICS)

1. Il Progetto

Il Dipartimento promuove e coordina l'attività di ricerca scientifica, teorica e applicata, tanto dal punto di vista descrittivo quanto dal punto di vista storico, nelle aree di ricerca che comprendono gli studi relativi alla teoria del linguaggio, alla linguistica storica e alla storia del pensiero linguistico; alla teoria della letteratura e alle letterature comparate; alle lingue, filologie e letterature classiche e medievali; alla linguistica, filologia e letteratura italiana; alle scienze dello spettacolo.

Il Dipartimento

- favorisce lo sviluppo di rapporti di collaborazione e scambio di docenti e studenti con altre Università sia nazionali sia internazionali;
- divulga i risultati della ricerca nel rispetto della libertà e dell'autonomia di ricerca e d'insegnamento di ogni singolo docente/ricercatore, cui sono riconosciuti pari dignità e il diritto di accedere ai finanziamenti per la ricerca;
- incoraggia e sostiene la partecipazione a progetti di ricerca nazionali e internazionali relativi alle tematiche caratterizzanti l'attività scientifica del Dipartimento.

2. In ragione di ciò le attività di ricerca che si svolgono all'interno del Dipartimento si focalizzano:

(a) sulla teoria e tipologia del linguaggio, sulla storia del pensiero linguistico e la linguistica storica; sulle relazioni tra lingue e società;

(b) sul problema generale della letteratura, dei generi, della produzione, della diffusione e valutazione dei testi, del confronto fra testi appartenenti a diverse letterature e culture;

(c) sulle letterature e le culture di lingua greca dal II millennio a.C. all'età contemporanea;

(d) sugli aspetti linguistici, filologici e letterari concernenti le opere e gli autori in lingua latina dalle origini all'età tardoantica, e la loro trasmissione e fortuna nelle età successive;

(e) sulla ricerca filologica sui testi greci e latini, antichi e tardoantichi, trasmessi dalla tradizione manoscritta antica e medievale, nonché sul teatro antico greco e latino, sulla fortuna della cultura antica, sulla storia degli studi classici e sulla didattica delle lingue classiche; sulle opere antiche di argomento cristiano sia in lingua greca sia in lingua latina e sulla loro tradizione;

(f) sulle opere in lingua latina di tutta l'area europea dalla fine dell'evo antico all'età umanistica; sulle origini e lo sviluppo delle lingue e delle letterature romanze con speciale riguardo al Medioevo;

(g) sulla lingua italiana e i dialetti parlati in Italia; sulla lingua letteraria e le sue strutture formali, la lessicografia e la grammaticografia, nonché su problemi e metodologie di didattica della lingua italiana;

(h) sulle opere e le dinamiche culturali della letteratura italiana dal Medioevo all'età contemporanea, e i relativi autori, nonché sulle opere in altra lingua prodotte nell'ambito del medesimo contesto storico-geografico; sulla filologia della letteratura italiana, aperta ai diversi aspetti dei testi, redatti nelle lingue di cultura dell'Europa occidentale (oltre ai volgari, il latino e il greco), prodotti in Italia o attinenti alla cultura italiana, dal Medioevo all'età contemporanea;

(i) sulle opere letterarie italiane a partire dagli eventi rivoluzionari tardo settecenteschi, nella lingua e nei dialetti italiani e sui relativi autori nonché sulle opere di autori italiani in lingue straniere;

(l) sullo spettacolo dal vivo, sulla musica di tradizione sia scritta sia orale, la fotografia, il cinema, la televisione e i media audiovisivi, indagati in prospettiva storica, critica, sistematica e organizzativa.

3. I SSD di riferimento, ai quali si fa riferimento per ogni ulteriore definizione, sono i seguenti:

AREA 10 – SCIENZE DELL'ANTICHITÀ, FILOLOGICO-LETTERARIE E STORICO-ARTISTICHE		
SSD approvati CUN 4.11.2009		*SSD attuali*
Macrosettore - Codice e denominazione	*SSD - Codice e denominazione*	
10/C MUSICA, TEATRO, CINEMA, TELEVISIONE E MEDIA AUDIOVISIVI	**10/C1 : TEATRO, MUSICA, CINEMA, TELEVISIONE E MEDIA AUDIOVISIVI**	L-ART/05 DISCIPLINE DELLO SPETTACOLO L-ART/06 CINEMA, FOTOGRAFIA E TELEVISIONE L-ART/07 MUSICOLOGIA E STORIA MUSICA L-ART/08 ETNOMUSICOLOGIA

10/D SCIENZE DELL'ANTICHITÀ	**10/D2 : LINGUA E LETTERATURA GRECA**	L-FIL-LET/01 CIVILTÀ EGEE L-FIL-LET/02 LINGUA E LETT. GRECA L-FIL-LET/07 CIVILTÀ BIZANTINA L-LIN/20 LINGUA E LETT. NEOGRECA L-FIL-LET/06 LETT. CRISTIANA ANTICA
	10/D3 : LINGUA E LETTERATURA LATINA	L-FIL-LET/04 LINGUA E LETT. LATINA L-FIL-LET/06 LETT. CRISTIANA ANTICA
	10/D4 : FILOLOGIA CLASSICA E TARDOANTICA	L-FIL-LET/05 FILOLOGIA CLASSICA L-FIL-LET/06 LETT. CRISTIANA ANTICA L-ANT/05 PAPIROLOGIA
10/E FILOLOGIE E LETTERATURE MEDIO-LATINA E ROMANZE	**10/E1 : FILOLOGIE E LETTERATURE MEDIO-LATINA E ROMANZE**	L-FIL-LET/08 LETTERATURA LATINA MEDIEVALE E UMANISTICA L-FIL-LET/09 FILOLOGIA E LINGUISTICA ROMANZA L-LIN/17 LINGUA E LETT. ROMENA L-LIN/08 LETTERATURA PORTOGHESE E BRASILIANA L-LIN/09 LINGUA E TRAD. – LINGUE PORTOGHESE E BRASILIANA
10/F ITALIANISTICA	**10/F1 : LETTERATURA ITALIANA E COMPARATA**	L-FIL-LET/10 LETTERATURA ITALIANA L-FIL-LET/13 FILOLOGIA DELLA LETTERATURA ITALIANA L-FIL-LET/14 CRITICA LETTERARIA E LETTERATURE COMPARATE
	10/F2 : LETTERATURA ITALIANA CONTEMPORANEA	L-FIL-LET/11 LETTERATURA ITALIANA CONTEMPOR.
	10/F3 : LINGUISTICA ITALIANA	L-FIL-LET-12 LINGUISTICA ITALIANA
10/G1 GLOTTOLOGIA E LINGUISTICA	**10/G1 : GLOTTOLOGIA E LINGUISTICA**	L-FIL-LET/03 FILOLOGIA ITALICA, ILLIRICA, CELTICA L-LIN/01 GLOTTOLOGIA E LINGUISTICA L-LIN/02 DIDATTICA DELLE LINGUE MODERNE L-LIN/18 LINGUA E LETT. ALBANESE

Dipartimento
LINGUE E LETTERATURE STRANIERE
(*FOREIGN LANGUAGES AND LITERATURES)*

1. Il Progetto

Il Dipartimento promuove e coordina l'attività di ricerca scientifica, teorica e applicata, tanto dal punto di vista descrittivo quanto dal punto di vista storico, nelle aree di ricerca che comprendono gli studi relativi alle lingue straniere e alle culture, alle opere letterarie e agli autori nelle lingue straniere.
Il Dipartimento

- favorisce lo sviluppo di rapporti di collaborazione e scambio di docenti e studenti con altre Università sia nazionali sia internazionali;
- divulga i risultati della ricerca nel rispetto della libertà e dell'autonomia di ricerca e d'insegnamento di ogni singolo docente/ricercatore, cui sono riconosciuti pari dignità e il diritto di accedere ai finanziamenti per la ricerca;
- incoraggia e sostiene la partecipazione a progetti di ricerca nazionali e internazionali relativi alle tematiche caratterizzanti l'attività scientifica del Dipartimento.

2. In ragione di ciò le attività di ricerca che si svolgono all'interno del Dipartimento si focalizzano:

(a) sull'analisi metalinguistica della lingua francese nelle sue diverse dimensioni sincroniche e diacroniche, nei suoi diversi aspetti, nelle sue strutture, nonché nei diversi livelli e registri di comunicazione orale e scritta e nelle sue varietà regionali, stilistiche, retoriche e letterarie, con attenzione anche alle problematiche della didattica e dei processi traduttivi; sugli studi sulla cultura e le opere letterarie in lingua francese dalle origini ai giorni nostri e sui relativi autori, tanto della madrepatria quanto dei paesi francofoni; sulle relazioni fra le letterature di lingua francese e le letterature delle minoranze etniche;
(b) sull'analisi metalinguistica della lingua spagnola nelle sue diverse dimensioni sincroniche e diacroniche, nei suoi diversi aspetti, nelle sue strutture, nonché nei diversi livelli e registri di comunicazione orale e scritta e nelle sue varietà regionali, stilistiche, retoriche e letterarie, con attenzione anche alle problematiche della didattica e dei processi traduttivi; sullo spagnolo d'America e nelle sue varianti regionali e nei suoi rapporti con le lingue amerindiane; sulla cultura e sulle opere letterarie in lingua spagnola dalle origini ai giorni nostri e sui relativi autori, tanto della madrepatria quanto dei paesi di lingua spagnola; sulle relazioni fra le letterature di lingua spagnola e le letterature delle minoranze etniche;
(c) sull'analisi metalinguistica della lingua inglese nelle sue diverse dimensioni sincroniche e diacroniche, nei suoi diversi aspetti, nelle sue strutture, nonché nei diversi livelli e registri di comunicazione orale e scritta; sulla lingua anglo-americana e le sue varietà regionali, stilistiche, retoriche e letterarie, con attenzione anche alle problematiche della didattica e dei processi traduttivi; sulle culture e letterature di lingua inglese e sui relativi autori, coprendo l'arco cronologico dalle origini ai giorni nostri; sulle relazioni fra la letteratura di lingua inglese e le letterature delle minoranze etniche;
(d) sull'analisi metalinguistica delle lingue di gruppo germanico nelle loro dimensioni sincroniche e diacroniche, nelle loro strutture nonché nei diversi livelli e registri di comunicazione orale e scritta e nelle loro varietà regionali, stilistiche, retoriche e letterarie, con attenzione anche alle problematiche della didattica e dei processi traduttivi; sulle culture, sui testi e sulle opere letterarie nelle lingue germaniche, dalle loro testimonianze più antiche a quelle contemporanee, nonché sui modi della loro trasmissione e sui loro autori;
(e) sull'analisi metalinguistica delle lingue di gruppo slavo nelle loro dimensioni sincroniche e diacroniche, nelle loro strutture nonché nei diversi livelli e registri di comunicazione orale e scritta e nelle loro varietà, stilistiche, retoriche e letterarie, con attenzione anche alle problematiche della didattica e dei processi traduttivi; sulle culture, sui testi e sulle opere letterarie in lingue slave, dalle loro testimonianze più antiche a quelle contemporanee, nonché sui modi della loro trasmissione e ai loro autori;
(f) sugli studi linguistici, filologici e letterari relativi al mondo islamico e all'Asia centrale e orientale (N.B.: settori attualmente non presenti nell'Università di Verona).

3. **I SSD di riferimento**, ai quali si fa riferimento per ogni ulteriore definizione, sono i seguenti:

AREA 10 – SCIENZE DELL'ANTICHITÀ, FILOLOGICO-LETTERARIE E STORICO-ARTISTICHE		
SSD approvati CUN 4.11.2009		*SSD attuali*
Macrosettore - Codice e denominazione	*SSD - Codice e denominazione*	
10/H FRANCESISTICA	**10/H1 : LINGUA, LETTERATURA E CULTURA FRANCESE**	L-LIN/03 LETTERATURA FRANCESE L-LIN/04 LINGUA E TRADUZIONE –LINGUA FRANCESE
10/I ISPANISTICA	**10/I1 : LINGUE, LETTERATURE E CULTURE SPAGNOLA E ISPANOAMERICANE**	L-LIN/05 LETTERATURA SPAGNOLA L-LIN/06 LINGUA E LETTERATURE ISPANOAMERICANE L-LIN/07 LINGUA E TRADUZIONE – LINGUA SPAGNOLA
10/L ANGLISTICA E ANGLOAMERICANISTICA	**10/L1 : LINGUE, LETTERATURE E CULTURE INGLESE E ANGLO-AMERICANA**	L-LIN/10 LETTERATURA INGLESE L-LIN/11 LINGUE E LETTERATURE ANGLOAMERICANE L-LIN/12 LINGUA E TRADUZIONE – LINGUA INGLESE
10/M LINGUE, LETTERATURE E CULTURE DELL'EUROPA NORD E CENTRO-ORIENTALE	**10/M1 : LINGUE, LETTERATURE E CULTURE GERMANICHE**	L-FIL-LET/15 FILOLOGIA GERMANICA L-LIN/13 LETTERATURA TEDESCA L-LIN/14 LINGUA E TRADUZIONE – LINGUA TEDESCA L-LIN/15 LINGUE E LETTERATURE NORDICHE L-LIN/16 LINGUA E LETTERATURA NEDERLANDESE L-LIN/19 FILOLOGIA UGRO-FINNICA
	10/M2 : SLAVISTICA	L-LIN/21 SLAVISTICA
10/N CIVILTÀ DELL'ORIENTE	**10/N2 : CULTURE DEL MONDO ISLAMICO**	L-OR/09 LINGUE E LETT. DELL'AFRICA L-OR/10 STORIA DEI PAESI ISLAMICI L-OR/11 ARCH. E ST. DELL'ARTE MUSULMANA L-OR/12 LINGUA E LETTERATURA ARABA L-OR/13 ARMENISTICA, CAUCASOLOGIA, MONGOLISTICA E TURCOLOGIA L-OR/14 FILOLOGIA, RELIGIONI E STORIA DELL'IRAN L-OR/15 LINGUA E LETTERATURA PERSIANA
	10/N3 : CIVILTÀ DELL'ASIA CENTRALE E ORIENTALE	L-OR/16 ARCH. E ST. DELL'ARTE DELL'INDIA E DELL'ASIA CENTRALE L-OR/17 FILOSOFIE, RELIGIONI E STORIA DELL'INDIA E DELL'ASIA CENTRALE L-OR/18 INDOLOGIA E TIBETOLOGIA L-OR/19 LINGUE E LETTERATURE MODERNE DEL SUBCONTINENTE INDIANO L-OR/20 ARCHEOLOGIA, STORIA DELL'ARTE E FILOSOFIE DELL'ASIA ORIENTALE L-OR/21 LINGUE E LETTERATURE DELLA CINA E DELL'ASIA SUD-ORIENTALE L-OR/22 LINGUE E LETTERATURE DEL GIAPPONE E DELLA COREA L-OR/23 STORIA DELL'ASIA OR. E SUD-OR.

Dipartimento
FILOSOFIA, PEDAGOGIA E PSICOLOGIA
(PHILOSOPHY, EDUCATION AND PSYCHOLOGY)

Specificità: Filosofia; filosofia e scienza politica; pedagogia; psicologia. Studio del pensiero filosofico e politico; studio della cultura educativa; studio dei processi psicologici. La ricerca filosofica nelle diverse epoche storiche e culturali e nei diversi ambiti tematici. Analisi teoretica e storica delle esperienze educative, ricerca empirica nei vari campi dell'educazione e della formazione. Prospettive teoriche e ricerca empirica sulle componenti soggettive e sociali di atteggiamenti, comportamenti, processi di comunicazione e di costruzione di conoscenza.

Al dipartimento afferiscono i docenti e i ricercatori dei seguenti macrosettori:
(a) 11/D: FILOSOFIA
(b) 14/A: TEORIA POLITICA
(c) 11/E: PEDAGOGIA
(d) 11/F: PSICOLOGIA (da /F1 a /F3).

Tali settori risultano collegati tra loro da una prospettiva centrata sul dialogo tra saperi teorici ed empirici in ordine a diversi ambiti della cultura e dell'esperienza umana. Ciò è reso evidente dalle declaratorie nel modo che segue.

Per quanto riguarda l'ambito della filosofia, il SSD 11/D1 propone un'idea di ricerca come confronto critico con esperienze culturali e discipline diverse, in cui la filosofia "si pone come interlocutrice di vari saperi, con l'obbiettivo di favorire l'approfondimento critico e l'interpretazione delle conoscenze". L'ambito della filosofia della scienza promuove la riflessione epistemologica, studiando le "connessioni tra ricerca filosofica e conoscenza scientifica" in diversi ambiti (11/D2). La filosofia morale studia l'agire dell'uomo nella sua dimensione morale, etico-sociale, politica e l'etica della comunicazione (11/D3). L'estetica intreccia la riflessione filosofica con pratiche e saperi artistici (11/D4). La filosofia del linguaggio studia "le diverse modalità e articolazioni che l'indagine sul linguaggio può assumere; affronta il ruolo che la dimensione linguistica riveste nel contesto di altri ambiti significativi dell'esperienza umana" (11/D4). Le storie della filosofia studiano la genesi e lo sviluppo storico del pensiero, "individuandone teorie, proposizioni e risultati in contesti socio-culturali definiti cronologicamente o individuati in rapporto a specifici orientamenti teorici" in diversi ambiti storico-culturali (11/D5).

Il macrosettore 14/A-Teoria politica ha per oggetto lo studio e la ricerca sui diversi aspetti della problematica politica secondo due prospettive, una eminentemente teorica (14/A1: filosofia politica) e un'altra seguendo il modello delle scienze empiriche (14/A2: scienze politiche).

Le scienze pedagogiche hanno come oggetto di ricerca le teorie dell'educazione e le esperienze educative considerate in una prospettiva temporale e spaziale, e si articolano come segue: ricerche di tipo "teoretico-fondativo ed epistemologico-metodologico"; ricerche empiriche "sulle attività educative connesse ai cambiamenti culturali e degli stili di vita e sulle implicazioni educative dei nuovi fenomeni sociali e interculturali" (11/E1); studi a carattere storico sul pensiero, le istituzioni e le pratiche educative (11/E1); ricerche a carattere applicativo e pragmatico che riguardano la didattica, le tecniche e le tecnologie educative a servizio dell'integrazione delle differenze (11/E2); studi e ricerche "con impostazione sperimentale, relative alla valutazione delle competenze e dei rendimenti scolastici e dei processi di formazione, (…) alla progettazione e alla valutazione degli interventi nei sistemi scolastici" (11/E2).

Per quanto riguarda l'ambito psicologico, il settore 11/F1 (psicologia generale, psicobiologia e psicometria) si interessa all'attività scientifica e didattico-formativa nei campi che hanno le competenze relative all'organizzazione del comportamento e delle principali funzioni psicologiche, includendo gli

studi da un lato della coscienza, della personalità e dell'intelligenza, dall'altro dei correlati biologici, fisiologici e neuropsicologici del comportamento, nonché le competenze caratteristiche della psicometria, attinenti alle teorie e alle procedure di misura nelle scienze psicologiche. Il settore 11/F2 (psicologia dello sviluppo e dell'educazione) promuove attività scientifica e didattico-formativa nel campo dello sviluppo delle competenze cognitive, linguistiche, sociali, affettive e relazionali e dei processi che lo determinano in una prospettiva ontogenetica che include l'intero arco della vita. Infine, il settore 11/F3 (psicologia sociale, del lavoro e delle organizzazioni) include le discipline volte a comprendere i fenomeni sociali, culturali, organizzativi ed economici, assumendo come punto di vista lo studio dei processi psicologici e relazionali che a diversi livelli influenzano il sistema delle rappresentazioni, cognizioni, emozioni, motivazioni ed azioni nei diversi sistemi e contesti di vita.

11/D-FILOSOFIA		
	11/D1-FILOSOFIA TEORETICA	**M-FIL/01-FILOSOFIA TEORETICA**
	11/D2-LOGICA, STORIA E FILOSOFIA DELLA SCIENZA	**M-FIL/02-LOGICA E FILOSOFIA DELLA SCIENZA** **M-STO/05-STORIA DELLE SCIENZE E DELLE TECNICHE**
	11/D3-FILOSOFIA MORALE	**M-FIL/03-FILOSOFIA MORALE**
	11/D4-ESTETICA E FILOSOFIA DEI LINGUAGGI	**M-FIL/05-FILOSOFIA E TEORIA DEI LINGUAGGI** **M-FIL/04-ESTETICA**
	11/D5-STORIA DELLA FILOSOFIA	**M-FIL/06- STORIA DELLA FILOSOFIA** **M-FIL/07- STORIA DELLA FILOSOFIA ANTICA** **M-FIL/08- STORIA DELLA FILOSOFIA MEDIOEVALE**
11/E-PEDAGOGIA		
	11/E1-PEDAGOGIA E STORIA DELLA PEDAGOGIA	**M/PED-01-PEDAGOGIA GENERALE E SOCIALE** **M/PED-02-STORIA DELLA PEDAGOGIA**
	11/E2-DIDATTICA, PEDAGOGIA SPECIALE E RICERCA EDUCATIVA	**M/PED-03-DIDATTICA E PEDAGOGIA SPECIALE** **M/PED-04-PEDAGOGIA SPERIMENTALE**
11/F-PSICOLOGIA		
	11/F1-PSICOLOGIA GENERALE, PSICOBIOLOGIA E PSICOMETRIA (*)	**M-PSI/01 – PSICOLOGIA GENERALE** **M-PSI/02 PSICOBIOLOGIA E PSICOLOGIA FISIOLOGICA** **M-PSI/03 PSICOMETRIA**
	11/F2 – PSICOLOGIA DELLO SVILUPPO E DELL'EDUCAZIONE	**M-PSI/04 – PSICOLOGIA DELLO SVILUPPO E DELL'EDUCAZIONE**
	11/F3 - PSICOLOGIA SOCIALE, DEL LAVORO E DELLE ORGANIZZAZIONI	**M-PSI/05 – PSICOLOGIA SOCIALE** **M-PSI/06 – PSICOLOGIA DEL LAVORO E DELLE ORGANIZZAZIONI**
14/A-TEORIA POLITICA		
	14/A1-FILOSOFIA POLITICA	**SPS/01 FILOSOFIA POLITICA**
	14/A2-SCIENZA POLITICA	**SPS/04-SCIENZA POLITICA**

Dipartimento
ECONOMIA AZIENDALE
(DEPARTMENT OF BUSINESS ADMINISTRATION)

1. Il Progetto

L'obiettivo del Dipartimento di Economia Aziendale è quello di promuovere la ricerca e la formazione nel campo delle discipline economico-aziendali (Area CUN 13 – Scienze Economiche e Statistiche), intese, definite ed identificate in base sia alla consolidata tradizione culturale degli studi in materia di impresa, sia alle più recenti tendenze evolutive emerse nei sistemi produttivi e sociali a livello nazionale ed internazionale, tra cui si colloca l'estensione dell'approccio aziendale a peculiari categorie di organizzazioni e sistemi, quali la pubblica amministrazione, le istituzioni internazionali e gli enti non profit.

Tali studi, facendo perno sui concetti di impresa e di azienda, sono oggi caratterizzati da:

1) complessità e globalità di approccio;
2) vastità dell'orizzonte oggetto delle analisi;
3) ampi elementi di interdisciplinarietà;
4) varietà di approccio metodologico.

In ragione di ciò, le attività di ricerca che si svolgono all'interno del Dipartimento:

1) si focalizzano sui fenomeni oggetto dell'approccio di analisi aziendale (principalmente imprese di tutti i settori, ma anche enti ed organizzazioni prive di scopo di lucro), colti nella loro naturale dimensione evolutiva e dinamica, estendendosi a considerare l'analisi degli specifici contesti in cui tali soggetti operano e dei fattori che li caratterizzano in modo peculiare;
2) hanno ad oggetto una vasta gamma di ambiti e di tematiche di ricerca, che tendono a confluire in approcci tesi a cogliere la portata dei processi evolutivi in atto a livello sia locale che globale;
3) presentano numerosi punti di contatto ed aspetti di complementarietà non solo al loro interno, ma anche nei confronti di aree tematiche contigue, ad esempio nei settori delle scienze economiche e socio- antropologiche, delle scienze giuridiche, e, in generale, delle discipline che studiano i processi di innovazione tecnologica;
4) si realizzano tramite approcci metodologici complessi, che tendono ad integrare l'analisi teorica con l'osservazione della realtà e la verifica empirica. In ragione di ciò, attività di ricerca focalizzate all'approfondimento specialistico di temi ben definiti ed individuati coesistono con indagini e studi miranti alla più vasta comprensione di fenomeni generali.

In coerenza con quanto sopra enunciato, all'interno del Dipartimento di Economia Aziendale vengono riconosciute le seguenti priorità di sviluppo:

1) alle attività di ricerca che consentano di cogliere la portata innovativa dei processi di trasformazione e di cambiamento nell'ambito delle attività d'impresa, della struttura e del funzionamento dei differenti comparti del sistema produttivo (sistema industriale, finanziario e delle attività di servizio) e delle dinamiche che emergono nel vasto comparto delle pubbliche amministrazioni e delle organizzazioni non profit.
2) alle attività caratterizzate da interdisciplinarietà di approccio e da valenza internazionale degli output conseguiti.

Il Dipartimento di Economia Aziendale prosegue le attività del preesistente dipartimento di Economia Aziendale istituito con decreto rettorale n. 1664 del 6 dicembre 2002.

2. I SSD di riferimento

I settori scientifico-disciplinari di naturale afferenza per il Dipartimento di Economia Aziendale sono quelli che riassumono le discipline derivanti dal duplice ceppo storico dell'Economia Aziendale/Ragioneria e della Tecnica Industriale e Commerciale; in sintesi:

Livello 2:AREA – 13 - SCIENZE ECONOMICHE E STATISTICHE

Livello 3	Livello 4	
Macrosettore Codice e Denominazione	**Settore Scientifico Disciplinare – S.S.D Codice e Denominazione**	VECCHIO S.S.D. Codice e Denominazione
13/B – ECONOMIA AZIENDALE		
	13/B1 – ECONOMIA AZIENDALE	SECS-P/07 – ECONOMIA AZIENDALE
	13/B2 – ECONOMIA E GESTIONE DELLE IMPRESE	SECS-P/08 – ECONOMIA E GESTIONE DELLE IMPRESE
	13/B3 – ORGANIZZAZIONE AZIENDALE	SECS-P/10 – ORGANIZZAZIONE AZIENDALE
	13/B4 – ECONOMIA DEGLI INTERMEDIARI FINANZIARI E FINANZA AZIENDALE	SECS-P/11 – ECONOMIA DEGLI INTERMEDIARI FINANZIARI SECS-P/09 – FINANZA AZIENDALE
	13/B5 – SCIENZE MERCEOLOGICHE	SECS-P/13 – SCIENZE MERCEOLOGICHE

Inoltre, in funzione della rilevanza assunta dall'analisi di fatti, processi e fenomeni economici, con particolare riferimento alla centralità di indagine relativa all'impresa ed al settore agricolo, costituisce settore di afferenza anche il seguente:

Livello 2:AREA 07 – SCIENZE AGRARIE E VETERINARIE

Livello 3	Livello 4	
Macrosettore Codice e Denominazione	**Settore Scientifico Disciplinare – S.S.D. Codice e Denominazione**	VECCHIO - S.S.D. Codice e Denominazione
07/A – ECONOMIA AGRARIA ED ESTIMO		
	07/A1 – ECONOMIA AGRARIA ED ESTIMO	AGR/01 – ECONOMIA ED ESTIMO RURALE

Dipartimento
SCIENZE ECONOMICHE
(DEPARTMENT OF ECONOMICS)

1. Il Progetto

Il Dipartimento promuove e coordina l'attività di ricerca scientifica, teorica e applicata, nell'ambito dell'Area CUN 13 – Scienze Economiche e Statistiche.

Le aree di ricerca comprendono la microeconomia e la macroeconomia, i temi legati allo sviluppo delle politiche economiche, lo studio dell'intervento pubblico nonché l'interazione tra il settore pubblico dell'economia ed il settore privato, l'analisi delle istituzioni economiche, lo sviluppo e l'utilizzo di strumenti statistici, econometrici e sperimentali per l'analisi dei fenomeni economici e finanziari, lo studio della struttura economica con particolare riferimento alle aree geografiche, ai settori produttivi e all'evoluzione demografica, l'analisi storico economica dei sistemi socio-economici preindustriali e industrializzati, lo studio dei metodi statistici per le scienze del sociale, lo sviluppo di metodi e strumenti matematici per la produzione di modelli relativi alle scienze economiche e sociali, alla finanza, alle scienze attuariali, alle scelte individuali, strategiche e collettive, all'analisi dei mercati, alla gestione del rischio.

Il Dipartimento:

- favorisce lo sviluppo di rapporti di collaborazione e scambio di docenti e studenti con altre Università sia nazionali sia internazionali;
- divulga i risultati della ricerca nel rispetto della libertà e dell'autonomia di ricerca e d'insegnamento di ogni singolo docente/ricercatore, cui sono riconosciuti pari dignità e il diritto di accedere direttamente ai finanziamenti per la ricerca;
- incoraggia e sostiene la partecipazione a progetti di ricerca nazionali e internazionali relativi ai più attuali temi economico-finanziari.

La promozione dell'attività di ricerca del Dipartimento si sviluppa anche attraverso Corsi di Dottorato di Ricerca. Seminari e convegni organizzati regolarmente assicurano la partecipazione e l'interazione con ricercatori e studiosi di fama internazionale.

Il Dipartimento di Scienze Economiche prosegue le attività del preesistente dipartimento di Scienze Economiche istituito con decreto rettorale n. 9691 del 26 giugno 1998.

2. I SSD di riferimento

Le ricerca del Dipartimento è sostenuta soprattutto da docenti/ricercatori afferenti ai seguenti settori scientifico-disciplinari:

Livello 2:AREA – 13 - SCIENZE ECONOMICHE E STATISTICHE

Livello 3	**Livello 4**	
Macrosettore **Codice e Denominazione**	**Settore Scientifico Disciplinare – S.S.D** **Codice e Denominazione**	VECCHIO S.S.D. Codice e Denominazione
13/A – ECONOMIA		
	13/A1 – ECONOMIA POLITICA	SECS-P/01 – ECONOMIA POLITICA
	13/A2 – POLITICA ECONOMICA	SECS-P/02 – POLITICA ECONOMICA
	13/A3 – SCIENZA DELLE FINANZE	SECS-P/03 – SCIENZA DELLE FINANZE

	13/A4 – ECONOMIA APPLICATA	SECS-P/06 – ECONOMIA APPLICATA
	13/A5 – ECONOMETRIA	SECS-P/05 – ECONOMETRIA
13/C - STORIA ECONOMICA		
	13/C1 – STORIA ECONOMICA	SECS-P/12 – STORIA ECONOMICA SECS-P/04 – STORIA DEL PENSIERO ECONOMICO
13/D – STATISTICA E METODI MATEMATICI PER LE DECISIONI		
	13/D1 – STATISTICA	SECS-S/01 – STATISTICA SECS-S/02 – STATISTICA PER LA RICERCA SPERIMENTALE E TECNOLOGICA
	13/D2 – STATISTICA ECONOMICA	SECS-S/03 – STATISTICA ECONOMICA
	13/D3 – DEMOGRAFIA E STATISTICA SOCIALE	SECS-S/04 – DEMOGRAFIA SECS-S/05 – STATISTICA SOCIALE
	13/D1 – METODI MATEMATICI DELL'ECONOMIA E DELLE SCIENZE ATTUARIALI E FINANZIARIE	SECS-S/06 – METODI MATEMATICI DELL'ECONOMIA E DELLE SCIENZE ATTUARIALI E FINANZIARIE

Dipartimento
SCIENZE GIURIDICHE
(DEPARTMENT OF LAW)

1. Progetto

Obiettivo del Dipartimento è di promuovere e svolgere l'attività di ricerca nell'ambito dell'Area CUN 12 -Scienze giuridiche.

Le attività di ricerca del Dipartimento riguardano soprattutto gli ambiti tematici del diritto privato, del diritto pubblico, costituzionale ed ecclesiastico, del diritto amministrativo, del diritto commerciale, della navigazione e del lavoro, del diritto dell'economia, dei mercati e tributario, del diritto internazionale pubblico e privato, dell'Unione Europea e comparato, del diritto processuale civile, del diritto penale e processuale penale, del diritto romano, della storia del diritto medievale e moderno e della filosofia del diritto.
Il Dipartimento prosegue linee di ricerca consolidate e incoraggia linee di ricerca innovative per metodi, contenuti ed obiettivi. Promuove prospettive di studio a forte caratterizzazione integrata ed interdisciplinare, anche attraverso l'interazione con altre aree disciplinari, quali ad esempio l'area delle scienze economiche e aziendali, quella delle discipline storiche e letterarie, quella delle scienze sociologiche, psicologiche, mediche.
Fra gli ambiti di ricerca caratterizzati da complessità e globalità di approccio, oltre che da ampi elementi di interdisciplinarietà, e che richiedono la confluenza di approcci metodologici diversi, il Dipartimento si propone in particolare di continuare e promuovere gli studi sulla pubblica amministrazione, sulla responsabilità sociale di impresa, sul controllo delle politiche sulla spesa pubblica e sulle entrate, sul governo dell'impresa, sulla regolazione dei mercati e sulla tutela della concorrenza, sulle devianze minorili e sull'esecuzione penale, sulla persona e le relazioni familiari, sulle discriminazioni e l'immigrazione, sulla storia del matrimonio e della famiglia, sulla storia del metodo, sulla gestione del territorio e dei beni culturali ed ambientali, sulla tutela dei consumatori e delle minoranze, sull'informazione, sull'editoria e il giornalismo, sulle problematiche connesse all'impiego delle nuove tecnologie, sulle prospettive di armonizzazione economica, sociale e giuridica in ambito europeo ed internazionale, sulle dinamiche di funzionamento delle istituzioni europee ed internazionali.

Il Dipartimento anche tramite le Sezioni e i Centri che vi afferiscono:

- divulga i risultati della ricerca, organizza e concorre all'organizzazione di seminari, conferenze e convegni a carattere scientifico, anche in collaborazione con altre strutture italiane e straniere;
- incoraggia e sostiene la partecipazione a progetti di ricerca nazionali e internazionali relativamente ai temi compresi nei propri ambiti di ricerca;
- promuove lo sviluppo di rapporti di collaborazione e scambio di studiosi con altre strutture italiane e straniere;
- stabilisce contratti e convenzioni con istituzioni ed enti pubblici e privati finalizzate allo svolgimento di attività di ricerca e consulenza, nel rispetto delle disposizioni di Ateneo;
- concorre, in collaborazione con le Facoltà richiedenti, all'attività didattica relativa alle discipline afferenti al Dipartimento medesimo.

La promozione dell'attività di ricerca del Dipartimento si sviluppa anche attraverso le biblioteche afferenti al Dipartimento e la collaborazione con la Scuola di Dottorato in Giurisprudenza.
Il Dipartimento di Scienze Giuridiche prosegue le attività dei preesistenti Dipartimento di Studi Giuridici e Dipartimento di Diritto dell'Economia.

2. I SSD di riferimento

Tra le discipline di interesse del Dipartimento rientrano in via prioritaria quelle appartenenti ai settori scientifico-disciplinari compresi nell'Area 12 CUN – Scienze giuridiche,

Livello 2: AREA – 12 - SCIENZE GIURIDICHE

S.S.D. ATTUALI	S.S.D. previsti dalla Proposta CUN di Revisione dei S.S.D.	
	Livello 4	**Livello 3**
Settore Scientifico Disciplinare – S.S.D. - Codice e Denominazione	**Settore Scientifico Disciplinare – S.S.D. Codice e Denominazione**	**Macrosettore Codice e Denominazione**
		12 /A- DIRITTO PRIVATO
IUS 01 DIRITTO PRIVATO	**12 /A1 DIRITTO PRIVATO**	
		12/B- DIRITTO DELL'ECONOMIA, DEI MERCATI E TRIBUTARIO
IUS 03 DIRITTO AGRARIO IUS 05 DIRITTO DELL'ECONOMIA	**12/B1 DIRITTO DELL'ECONOMIA E DEI MERCATI FINANZIARI ED AGROALIMENTARI**	
IUS 12 DIRITTO TRIBUTARIO	**12 /B2 DIRITTO TRIBUTARIO**	
		12/C - DIRITTO COMMERCIALE, DELLA NAVIGAZIONE E DEL LAVORO
IUS 04 DIRITTO COMMERCIALE IUS 06 DIRITTO DELLA NAVIGAZIONE	**12/C1 DIRITTO COMMERCIALE E DELLA NAVIGAZIONE**	
IUS 07 DIRITTO DEL LAVORO	**12/C2 DIRITTO DEL LAVORO**	
		12/D - DIRITTO PUBBLICO, COSTITUZIONALE ED ECCLESIASTICO
IUS 08 DIRITTO COSTITUZIONALE IUS 09 ISTITUZIONI DI DIRITTO PUBBLICO	**12/D1 DIRITTO PUBBLICO E COSTITUZIONALE**	
IUS 11 DIRITTO ECCLESIASTICO E CANONICO	**12/D2 DIRITTO ECCLESIASTICO E CANONICO**	
		12/E - DIRITTO AMMINISTRATIVO
IUS 10 DIRITTO AMMINISTRATIVO	**12/E1 DIRITTO AMMINISTRATIVO**	
		12/F - DIRITTO INTERNAZIONALE, DELL'UNIONE EUROPEA E COMPARATO
IUS 13 DIRITTO INTERNAZIONALE IUS 14 DIRITTO DELL'UNIONE EUROPEA	**12 /F1 DIRITTO INTERNAZIONALE E DELL'UNIONE EUROPEA**	
IUS 02 DIRITTO PRIVATO COMPARATO IUS 21 DIRITTO PUBBLICO COMPARATO	**12/F2 DIRITTO COMPARATO**	
		12/G - DIRITTO PROCESSUALE CIVILE
IUS 15 DIRITTO PROCESSUALE CIVILE	**12/G1 DIRITTO PROCESSUALE CIVILE**	
		12/H - DIRITTO PENALE E PROCESSUALE PENALE
IUS 17 DIRITTO PENALE	**12/H 1 DIRITTO PENALE**	
IUS 16 DIRITTO PROCESSUALE PENALE	**12/H 2 DIRITTO PROCESSUALE PENALE**	
		12/I - DIRITTO ROMANO, STORIA DEL DIRITTO MEDIEVALE E MODERNO E FILOSOFIA DEL DIRITTO
IUS 18 DIRITTO ROMANO E DIRITTI DELL'ANTICHITÀ	**12/I 1 DIRITTO ROMANO E DIRITTI DELL'ANTICHITÀ**	
IUS 19 STORIA DEL DIRITTO MEDIEVALE E MODERNO	**12/I 2 STORIA DEL DIRITTO MEDIEVALE E MODERNO**	
IUS 20 FILOSOFIA DEL DIRITTO	**12/I 3 FILOSOFIA DEL DIRITTO**	

Dipartimento
CHIRURGIA
(DEPARTMENT OF SURGERY)

1. Il Progetto

Specificità: promozione e coordinamento dell'attività di ricerca scientifica, teorica e applicata, e ottimizzazione dell'interazione tra ricerca, assistenza e didattica nell'ambito chirurgico, generale e specialistico, e anestesiologico

Il Dipartimento realizza le proprie specificità attraverso l'interazione didattica e scientifica relativa alle conoscenze fisiopatologiche, all'approccio metodologico chirurgico e anestesiologico e alle applicazioni clinico-terapeutiche nelle malattie chirurgiche generali e specialistiche, oncologiche e non, dell'età adulta e pediatrica, con particolare riguardo agli ambiti goastroenterico, epato-bilio-pancreatico, toracico, vascolare, mammario, cardiaco, urologico, odontostomatologico e maxillo-facciale, otorinolaringoiatrico, neurochirurgico, ortopedico e riabilitativo, plastica ricostruttiva, terapie intensive.

Per il conseguimento dei propri obiettivi il Dipartimento:

- favorisce lo sviluppo di rapporti di collaborazione e scambio di docenti e studenti con altre Università sia nazionali sia internazionali;
- incoraggia e sostiene la partecipazione a progetti di ricerca nazionali e internazionali relativi ai più attuali temi di riferimento chirurgico generale e specialistico
- promuove l'attività di ricerca tramite Corsi di Dottorato di Ricerca e Scuole di Specializzazione per i quali sono organizzati regolarmente seminari e convegni (con la partecipazione di ricercatori e studiosi di fama internazionale).

2. I SSD di riferimento

Le ricerca del Dipartimento è sostenuta soprattutto da docenti/ricercatori afferenti ai seguenti settori scientifico-disciplinari:

Livello 2: AREA – 06 – SCIENZE MEDICHE

LIVELLO 3	LIVELLO 4	
MACROSETTORE CODICE E DENOMINAZIONE	SETTORE SCIENTIFICO DISCIPLINARE — S.S.D. CODICE E DENOMINAZIONE	VECCHIO S.S.D. CODICE E DENOMINAZIONE
06/C - CLINICA CHIRURGICA GENERALE		
	06/C1 - CHIRURGIA GENERALE	MED/18 CHIRURGIA GENERALE
06/E- CLINICA CHIRURGICA SPECIALISTICA		
	06/E1 - CHIRURGIA CARDIO-TORACO-VASCOLARE	MED/22 CHIRURGIA VASCOLARE MED/23 CHIRURGIA CARDIACA MED/21 CHIRURGIA TORACICA
	06/E2 CHIRURGIA PLASTICA-RICOSTRUTTIVA E CHIRURGIA PEDIATRICA	MED/19 CHIRURGIA PLASTICA MED/20 CHIRURGIA PEDIATRICA E INFANTILE
	06/E3 UROLOGIA	MED/24 UROLOGIA
	06/E4 - NEUROCHIRURGIA E CHIRURGIA	MED/27 NEUROCHIRURGIA

	MAXILLO FACCIALE	MED/29 CHIRURGIA MAXILLOFACCIALE
06/F- CLINICA CHIRURGICA INTEGRATA		
	06/F1 - MALATTIE ODONTOSTOMATOLOGICHE	MED/28 MALATTIE ODONTOSTOMATOLOGICHE
	06/F3- OTORINOLARINGOIATRIA E AUDIOLOGIA	MED/31 OTORINOLARINGOIATRIA MED/32 AUDIOLOGIA
	06/F4 - MALATTIE APPARATO LOCOMOTORE E MEDICINA FISICA E RIABILITATIVA	MED/33 MALATTIE APPARATO LOCOMOTORE MED/34 MEDICINA FISICA E RIABILITATIVA
06/L — CLINICA ANESTESIOLOGICA		
	06/L1 - ANESTESIOLOGIA	MED/41 ANESTESIOLOGIA
06/N — PROFESSIONI SANITARIE E TECNOLOGIE MEDICHE APPLICATE		
	06/N1- SCIENZE DELLE PROFESSIONI SANITARIE E DELLE TECNOLOGIE MEDICHE APPLICATE	MED/46 SCIENZE TECNICHE DI MEDICINA DI LABORATORIO MED/48 SCIENZE INFERMIERISTICHE E TECNICHE NEURO-PSICHIATRICHE E RIABILITATIVE MED/47 SCIENZE INFERMIERISTICHE OSTETRICO-GINECOLOGICHE MED/50 SCIENZE TECNICHE MEDICHE APPLICATE

Dipartimento
MEDICINA
(DEPARTMENT OF MEDICINE)

1. Il Progetto

Specificità: coordinamento dell'attività di ricerca scientifica clinica e sperimentale e ottimizzazione dell'interazione tra ricerca, assistenza e didattica nell'ambito della medicina interna e delle specialità mediche

Il Dipartimento realizza le proprie specificità attraverso la condivisione dell'approccio scientifico alle conoscenze fisiopatologiche e clinico-terapeutiche delle malattie internistiche generali e specialistiche dell'età adulta e geriatrica, con particolare riguardo a quelle cardiovascolari, dermatologiche, ematologiche, endocrine, gastroenterologiche, infettive, metaboliche, nefrologiche, oncologiche, polmonari e reumatologiche.

2. I SSD di riferimento

Le ricerca del Dipartimento è sostenuta soprattutto da docenti/ricercatori afferenti ai seguenti settori scientifico-disciplinari:

Livello 2: AREA – 06 – SCIENZE MEDICHE

LIVELLO 3	LIVELLO 4	
MACROSETTORE CODICE E DENOMINAZIONE	SETTORE SCIENTIFICO DISCIPLINARE — S.S.D. CODICE E DENOMINAZIONE	VECCHIO S.S.D. CODICE E DENOMINAZIONE
06/B - CLINICA MEDICA GENERALE		
	06/B1 - MEDICINA INTERNA	MED/09 MEDICINA INTERNA
06/D - CLINICA MEDICA SPECIALISTICA		
	06/D1 - MALATTIE DELL'APPARATO CARDIOVASCOLARE E MALATTIE DELL'APPARATO RESPIRATORIO	MED/10 MALATTIE DELL'APPARATO RESPIRATORIO MED/11 MALATTIE DELL'APPARATO CARDIO VASCOLARE
	06/D2 - GASTROENTEROLOGIA	MED/12 GASTROENTEROLOGIA
	06/D3 - ENDOCRINOLOGIA, NEFROLOGIA E SCIENZE DELLA ALIMENTAZIONE E DEL BENESSERE	MED/13 ENDOCRINOLOGIA MED/49 SCIENZE TECNICHE DIETETICHE APPLICATE MED/14 NEFROLOGIA
	06/D4 - MALATTIE DEL SANGUE, REUMATOLOGIA E ONCOLOGIA	MED/15 MALATTIE DEL SANGUE MED/16 REUMATOLOGIA MED/06 ONCOLOGIA MEDICA
	06/D5 - MALATTIE CUTANEE E VENEREE E MALATTIE INFETTIVE	MED/17 MALATTIE INFETTIVE MED/35 MALATTIE CUTANEE E VENEREE

Dipartimento
SCIENZE NEUROLOGICHE, NEUROPSICOLOGICHE, MORFOLOGICHE E MOTORIE
(DEPARTMENT OF NEUROLOGICAL, NEUROPSYCHOLOGICAL, MORPHOLOGICAL AND MOVEMENT SCIENCES)

1. Il Progetto

Specificità: coordinamento dell'attività di ricerca scientifica sperimentale e clinica e ottimizzazione delle interazioni tra ricerca e didattica nell'ambito di discipline caratterizzate da un'ampia condivisione di affinità culturali e/o approcci metodologici, riguardanti: la fisiologia umana; le scienze morfologiche macro e microscopiche; le malattie del sistema nervoso e dell'apparato visivo; le funzioni fisiologiche e biologico-molecolari del movimento umano; l'organizzazione del comportamento e delle principali funzioni psicologiche, includendo gli studi da un lato della coscienza, della personalità e dell'intelligenza, dall'altro dei correlati biologici, fisiologici e neuropsicologici del comportamento, nonché le competenze caratteristiche della psicometria, attinenti alle teorie e alle procedure di misura nelle scienze psicologiche.

Il Dipartimento:

- favorisce lo sviluppo di rapporti di collaborazione e scambio di docenti e studenti con altre Università sia nazionali sia internazionali;
- divulga i risultati della ricerca nel rispetto della libertà e dell'autonomia di ricerca e d'insegnamento di ogni singolo docente/ricercatore, cui sono riconosciuti pari dignità e il diritto di accedere direttamente ai finanziamenti per la ricerca;
- incoraggia e sostiene la partecipazione a progetti di ricerca nazionali ed internazionali relativi ai più attuali temi scientifici.

La promozione dell'attività di ricerca del Dipartimento si sviluppa anche attraverso Corsi di Dottorato di ricerca. Seminari e Convegni organizzati regolarmente assicurano la partecipazione e l'interazione con ricercatori e studiosi di fama internazionale.

Livello 2: AREA – 05 – SCIENZE BIOLOGICHE **AREA – 06 – SCIENZE MEDICHE**

AREA – 11 – DELLE SCIENZE STORICHE, FILOSOFICHE, PEDAGOGICHE, PSICOLOGICHE

LIVELLO 3	LIVELLO 4	
MACROSETTORE CODICE E DENOMINAZIONE	SETTORE SCIENTIFICO DISCIPLINARE — S.S.D. CODICE E DENOMINAZIONE	VECCHIO S.S.D. CODICE E DENOMINAZIONE
05/D- FISIOLOGIA		
	05/D1 — FISIOLOGIA	BIO/09 — FISIOLOGIA
05/H- ANATOMIA UMANA E ISTOLOGIA		
	05/ H1 - ANATOMIA UMANA	BIO/16 - ANATOMIA UMANA
	05/H2 - ISTOLOGIA	BIO/17 - ISTOLOGIA
06/D - CLINICA MEDICA SPECIALISTICA		
	06/D7 - NEUROLOGIA	MED/26 NEUROLOGIA
06/F- CLINICA CHIRURGICA INTEGRATA		
	06/F2 - MALATTIE APPARATO VISIVO	MED/30 MALATTIE APPARATO VISIVO
11/E- PEDAGOGIA		
	11/E2 – DIDATTICA, PEDAGOGIA SPECIALE E RICERCA EDUCATIVA	M-EDF/01 – METODI E DIDATTICHE DELLE ATTIVITA' MOTORIE M-EDF/02 – METODI E DIDATTICHE DELLE ATTIVITA' SPORTIVE
11/F- PSICOLOGIA		
	11/F1 - PSICOLOGIA GENERALE, PSICOBIOLOGIA E PSICOMETRIA (*)	M-PSI/01 - PSICOLOGIA GENERALE M-PSI/02 PSICOBIOLOGIA E PSICOLOGIA FISIOLOGICA M-PSI/03 PSICOMETRIA

Dipartimento
SANITA' PUBBLICA E MEDICINA DI COMUNITA'
(DEPARTMENT OF PUBLIC HEALTH AND COMMUNITY MEDICINE)

1. Il Progetto

Specificità: Promozione e coordinamento dell'attività di ricerca, teorica e applicata, miglioramento continuo dell'interazione ed integrazione tra ricerca, assistenza e didattica nell'ambito della Sanità Pubblica e di tutti i livelli delle reti della Medicina di Comunità.

Al DSPMC *(PHCMD)* afferiscono le attività di ricerca, didattica, organizzative ed assistenziali proprie degli ambiti di: prevenzione e sicurezza negli ambienti di vita e di lavoro; sorveglianza sanitaria ed ergonomia; gestione del rischio, sicurezza del paziente e valutazione della responsabilità in sanità; valutazione della qualità nelle reti dell'assistenza socio sanitaria; organizzazione, programmazione, management ed economia sanitaria; metodologia ed organizzazione della professione infermieristica; comunicazione in medicina; organizzazione, gestione e valutazione dei servizi di salute mentale, psichiatria clinica e psicosomatica; psichiatria epidemiologica e sociale; metodi di studio e tecniche di intervento che caratterizzano le applicazioni cliniche della psicologia a persone, gruppi, sistemi, per la soluzione dei loro problemi; nei campi della salute e sanitario, del disagio psicologico e delle psicopatologie competenze volte all'analisi e soluzione di problemi tramite interventi di valutazione, prevenzione, riabilitazione psicologica e psicoterapia; psicofarmacologia clinica; farmacoepidemiologia e farmacovigilanza; valutazione delle tecnologie sanitarie, del farmaco e del profilo farmacodinamico-cinetico dei chemioterapici; farmacologia traslazionale preclinica e clinica per la farmacoterapia e la prevenzione primaria; epidemiologia generale e clinica; statistica medica; determinanti di salute, benessere e stili di vita; igiene generale, dell'ambiente e degli alimenti; medicina legale e scienze forensi, criminologia, medicina sociale ed assicurativa, tossicologia forense, deontologia e bioetica medica.

2. I SSD di riferimento

Le ricerca del Dipartimento è sostenuta soprattutto da docenti/ricercatori afferenti ai seguenti settori scientifico-disciplinari:

Livello 2: AREA – 05 – SCIENZE BIOLOGICHE **AREA – 06 – SCIENZE MEDICHE**

AREA – 11 – DELLE SCIENZE STORICHE, FILOSOFICHE, PEDAGOGICHE, PSICOLOGICHE

LIVELLO 3	LIVELLO 4	
MACROSETTORE CODICE E DENOMINAZIONE	SETTORE SCIENTIFICO DISCIPLINARE — S.S.D. CODICE E DENOMINAZIONE	VECCHIO S.S.D. CODICE E DENOMINAZIONE
05/G - SCIENZE FARMACOLOGICHE SPERIMENTALI E CLINICHE		
	05/G1 – FARMACOLOGIA, FARMACOLOGIA CLINICA E FARMACODIAGNOSTICA	BIO/14 – FARMACOLOGIA BIO/15 BIOLOGIA FARMACEUTICA
06/M — SANITA' PUBBLICA		
	06/M1 - IGIENE GENERALE E APPLICATA E STATISTICA MEDICA	MED/42 IGIENE GENERALE E APPLICATA MED/01 STATISTICA MEDICA
	06/M2 - MEDICINA LEGALE	MED/43 MEDICINA LEGALE
	06/M3 - MEDICINA DEL LAVORO	MED/44 MEDICINA DEL LAVORO
06/D - CLINICA MEDICA SPECIALISTICA		
	06/D6 - PSICHIATRIA	MED/25 PSICHIATRIA
06/N — PROFESSIONI SANITARIE E TECNOLOGIE		

MEDICHE APPLICATE		
	06/N2 – SCIENZE INFERMIERISTICHE	MED/45 SCIENZE INFERMIERISTICHE GENERALI, CLINICHE E PEDIATRICHE
11/F- PSICOLOGIA		
	11/ F4- PSICOLOGIA CLINICA E DINAMICA	M-PSI /08- PSICOLOGIA CLINICA M-PSI/07 PSICOLOGIA DINAMICA

Dipartimento
PATOLOGIA E DIAGNOSTICA
(DEPARTMENT OF PATHOLOGY AND DIAGNOSTICS)

1. Il Progetto

Specificità: Studio dei meccanismi cellulari e molecolari di patologia e sviluppo ed applicazione di metodologie di diagnosi di patologie.

Il Dipartimento promuove lo sviluppo di attività di ricerca orientate a definire: a) i meccanismi molecolari del danno cellulare e d'organo alla base di processi patologici; b) i meccanismi molecolari e cellulari responsabili dello sviluppo di risposte di tipo innato o adattivo implicate nella difesa contro agenti patogeni e nella patologia autoimmune; c) i meccanismi molecolari della trasformazione neoplastica e delle alterazioni caratteristiche del loro fenotipo; d) i fattori che regolano l'interazione ospite-parassita dal punto di vista dell'azione patogena e della resistenza ai farmaci e) metodologie avanzate anatomo-patologiche, microbiologiche, laboratoristiche e d'immagine finalizzate alla diagnosi e al trattamento di patologie umane.

2. I SSD di riferimento

Le ricerca del Dipartimento è sostenuta soprattutto da docenti/ricercatori afferenti ai seguenti settori scientifico-disciplinari:

Livello 2: AREA – 06 – SCIENZE MEDICHE

LIVELLO 3	LIVELLO 4	
MACROSETTORE CODICE E DENOMINAZIONE	SETTORE SCIENTIFICO DISCIPLINARE — S.S.D. CODICE E DENOMINAZIONE	VECCHIO S.S.D. CODICE E DENOMINAZIONE
06/A - PATOLOGIA E DIAGNOSTICA DI LABORATORIO		
	06/A2 - PATOLOGIA GENERALE E PATOLOGIA CLINICA	MED/04 PATOLOGIA GENERALE MED/05 PATOLOGIA CLINICA MED/46 SCIENZE TECNICHE DI MEDICINA DI LABORATORIO MED/02 STORIA DELLA MEDICINA
	06/A3 - MICROBIOLOGIA E MICROBIOLOGIA CLINICA	MED/07 MICROBIOLOGIA E MICROBIOLOGIA CLINICA
	06/A4 - ANATOMIA PATOLOGICA	MED/08 ANATOMIA PATOLOGICA
06/I - CLINICA RADIOLOGICA		
	06/I1 - DIAGNOSTICA PER IMMAGINI, RADIOTERAPIA E NEURORADIOLOGIA	MED/36 DIAGNOSTICA PER IMMAGINI E RADIOTERAPIA MED/37 NEURORADIOLOGIA

Dipartimento
SCIENZE DELLA VITA E DELLA RIPRODUZIONE
(DEPARTMENT OF LIFE AND REPRODUCTION SCIENCES)

Il Progetto

Specificità: Il dipartimento di Scienze della Vita e della Riproduzione si occupa delle attività scientifiche, didattiche e organizzative nell'area delle scienze biomediche e della salute della donna e del bambino in ogni fase della vita.

Il dipartimento realizza le proprie specificità attraverso la condivisione dell'approccio sperimentale alle conoscenze biologiche applicate alla medicina, con particolare riguardo agli aspetti genetici, molecolari, biochimici, biochimici clinici, e alle malattie ostetriche e ginecologiche, neonatali e pediatriche.

I SSD di riferimento

Le ricerca del Dipartimento è sostenuta soprattutto da docenti/ricercatori afferenti ai seguenti settori scientifico-disciplinari:

Livello 2: AREA – 05- SCIENZE BIOLOGICHE **AREA – 06 – SCIENZE MEDICHE**

LIVELLO 3	LIVELLO 4	
MACROSETTORE CODICE E DENOMINAZIONE	SETTORE SCIENTIFICO DISCIPLINARE — S.S.D. CODICE E DENOMINAZIONE	VECCHIO S.S.D. CODICE E DENOMINAZIONE
05/E - BIOCHIMICA E BIOLOGIA MOLECOLARE SPERIMENTALI E CLINICHE		
	05/E1-BIOCHIMICA GENERALE E BIOCHIMICA CLINICA (*)	BIO/10 - BIOCHIMICA BIO/12 - BIOCHIMICA CLINICA E BIOLOGIA MOLECOLARE E CLINICA
	05/E2- BIOLOGIA MOLECOLARE (*)	BIO/11 – BIOLOGIA MOLECOLARE
05/F - BIOLOGIA APPLICATA		
	05/F1- BIOLOGIA APPLICATA	BIO/13 - BIOLOGIA APPLICATA
06/A - PATOLOGIA E DIAGNOSTICA DI LABORATORIO		
	06/A1 - GENETICA MEDICA	MED/03 GENETICA MEDICA
06/G— CLINICA PEDIATRICA		
	06/G1 - PEDIATRIA GENERALE, SPECIALISTICA E NEUROPSICHIATRIA INFANTILE	MED/38 PEDIATRIA GENERALE E SPECIALISTICA MED/39 NEUROPSICHIATRIA INFANTILE
06/ H - CLINICA GINECOLOGICA		
	06/H1 - GINECOLOGIA E OSTETRICIA	MED/40 GINECOLOGIA E OSTETRICIA

Dipartimento
INFORMATICA
(DEPARTMENT OF COMPUTER SCIENCE)

1. Il Progetto

Il Dipartimento promuove e coordina l'attività di ricerca scientifica, teorica e applicata, nell'ambito delle Aree CUN: 01 – SCIENZE MATEMATICHE E INFORMATICHE, 02 – SCIENZE FISICHE, e 09 – INGEGNERIA INDUSTRIALE E DELL'INFORMAZIONE.

Il dipartimento di Informatica promuove la ricerca scientifica nelle seguenti aree: logica matematica e matematiche complementari, geometria ed algebra, analisi matematica, probabilità e statistica matematica, fisica matematica, analisi numerica, ricerca operativa, informatica, fisica sperimentale delle interazioni fondamentali, fisica teorica delle interazioni fondamentali, fisica sperimentale della materia, fisica teorica della materia, fisica applicata, automatica, bioignegneria, e sistemi di elaborazione delle informazioni. Di queste aree sono particolarmente enfatizzati e sviluppati gli aspetti modellistici, computazionali, algoritmici e di processo in ambiti sia teorici che applicati.

Il Dipartimento di Informatica prosegue le attività del preesistente dipartimento di Informatica istituito con decreto rettorale n. 12237 del 08 maggio 2001.

2. I SSD di riferimento

Le ricerca del Dipartimento è sostenuta soprattutto da docenti/ricercatori afferenti ai seguenti settori scientifico-disciplinari:

Livello 2: AREA – 01 - SCIENZE MATEMATICHE E INFORMATICHE

Livello 3	**Livello 4**	
Macrosettore **Codice e Denominazione**	**Settore Scientifico Disciplinare – S.S.D.** **Codice e Denominazione**	VECCHIO S.S.D. Codice e Denominazione
01/A - MATEMATICA		
	01/A1 – LOGICA MATEMATICA E MATEMATICHE COMPLEMENTARI;	MAT/01 - LOGICA MATEMATICA MAT/04 - MATEMATICHE COMPLEMENTARI
	01/A2 – GEOMETRIA E ALGEBRA	MAT/02 - ALGEBRA MAT/03 - GEOMETRIA
	01/A3 - ANALISI MATEMATICA, PROBABILITÀ' E STATISTICA MATEMATICA	MAT/05 - ANALISI MATEMATICA MAT/06 - PROBABILITÀ E STATISTICA MATEMATICA
	01/A4 - FISICA MATEMATICA	MAT/07 - FISICA MATEMATICA
	01/A5 - ANALISI NUMERICA	MAT/08 - ANALISI NUMERICA
	01/A6 - RICERCA OPERATIVA	MAT/09 - RICERCA OPERATIVA
01/B - INFORMATICA		
	01/B1 - INFORMATICA	INF/01 - INFORMATICA

Livello 2: AREA – 02 - SCIENZE FISICHE

Livello 3	**Livello 4**	
Macrosettore **Codice e Denominazione**	**Settore Scientifico Disciplinare – S.S.D.** **Codice e Denominazione**	VECCHIO S.S.D. Codice e Denominazione
02/A – FISICA DELLE INTERAZIONI FONDAMENTALI		
	02/A1 – FISICA SPERIMENTALE DELLE INTERAZIONI FONDAMENTALI	FIS/01 – FISICA SPERIMENTALE FIS/04 – FISICA NUCLEARE E SUBNUCLEARE
	02/A2 – FISICA TEORICA DELLE INTERAZIONI FONDAMENTALI	FIS/02 – FISICA TEORICA MODELLI E METODI MATEMATICI FIS/04 – FISICA NUCLEARE E SUBNUCLEARE FIS/08 – DIDATTICA E STORIA DELLA

		FISICA
02/B – FISICA DELLA MATERIA		
	02/B1 - FISICA SPERIMENTALE DELLA MATERIA	FIS/01 – FISICA SPERIMENTALE FIS/03 – FISICA DELLA MATERIA
	02/B2 - FISICA TEORICA DELLA MATERIA	FIS/02 – FISICA TEORICA MODELLI E METODI MATEMATICI FIS/03 – FISICA DELLA MATERIA FIS/08 – DIDATTICA E STORIA DELLA FISICA
	02/B3 - FISICA APPLICATA	FIS/07 – FISICA APPLICATA (A BENI CULTURALI, AMBIENTALI, BIOLOGIA E MEDICINA)

Livello 2: AREA – 09 – INGEGNERIA INDUSTRIALE E DELL'INFORMAZIONE

09/G – INGEGNERIA DEI SISTEMI E BIOINGEGNERIA		
	09/G1 – AUTOMATICA	ING-INF/04 AUTOMATICA
	09/G2 – BIOINGEGNERIA	ING-INF/06 BIOINGEGNERIA ELETTRONICA E INFORMATICA ING-IND/34 BIOINGEGNERIA INDUSTRIALE
9/H – INGEGNERIA INFORMATICA		
	09/H1 – SISTEMI DI ELABORAZIONE DELLE INFORMAZIONI	ING-INF/05 SISTEMI DI ELABORAZIONE DELLE INFORMAZIONI

Dipartimento
BIOTECNOLOGIE
(DEPARTMENT OF BIOTECHNOLOGY)

1. Il Progetto

Il Dipartimento promuove e coordina l'attività di ricerca scientifica, teorica e applicata, nell'ambito delle Aree CUN: 03 – SCIENZE CHIMICHE, 05 – SCIENZE BIOLOGICHE, 07 – SCIENZE AGRARIE E VETERINARIE e 09 – INGEGNERIA INDUSTRIALE E DELL'INFORMAZIONE.

Il dipartimento di Biotecnologie promuove la ricerca scientifica nelle seguenti aree: chimica analitica, modelli e metodologie per le scienze chimiche, fondamenti delle scienze chimiche e sistemi inorganici, fondamenti chimici delle tecnologie, chimica organica, chimica industriale, chimica e tecnologie farmaceutiche, tossicologiche e nutraceutico-alimentari, botanica, fisiologia vegetale, ecologia, biochimica, biologia molecolare, genetica, microbiologia, arboricoltura generale, patologia vegetale, chimica e genetica agraria, scienze e tecnologie alimentari, microbiologia agraria, impianti e processi industriali chimici. Di queste aree sono particolarmente enfatizzati e sviluppati gli aspetti fondamentali legati ai processi ed alle tecnologie chimiche, biochimiche, e biologiche (molecolari, genetiche e micobiologiche) con applicazioni multidisciplinari in ambito vegetale, agro-alimentare, industriale, ambientale ed animale.

Il Dipartimento di Biotecnologie prosegue le attività del preesistente dipartimento di Biotecnologie, istituito con decreto rettorale n. 9696 del 26/06/1998 e successivamente modificato con decreto rettorale n. 3544 del 30/09/2008, e del Dipartimento di Scienze, Tecnologie e Mercati della Vite e del Vino (DiSTeMeV), istituito con decreto rettorale n. 706-2007 del 12/03/2007, per quanto concerne le attività scientifiche relative ai macrosettori: 07/B, 07/D, 07/E e 07/F.

2. I SSD di riferimento

Le ricerca del Dipartimento è sostenuta soprattutto da docenti/ricercatori afferenti ai seguenti settori scientifico-disciplinari:

Livello 2: AREA - 03 - SCIENZE CHIMICHE

Livello 3	**Livello 4**	
Macrosettore Codice e Denominazione	**Settore Scientifico Disciplinare - S.S.D. Codice e denominazione**	**VECCHIO S.S.D. Codice e Denominazione**
03/A – ANALITICO, CHIMICO-FISICO		
	03/A1 – CHIMICA ANALITICA	CHIM/01 – CHIMICA ANALITICA CHIM/12 CHIMICA DELL'AMBIENTE DEI BENI CULTURALI
	03/A2 – MODELLI E METODOLOGIE PER LE SCIENZE CHIMICHE	CHIM/02 – CHIMICA FISICA CHIM/12 – CHIMICA DELL'AMBIENTE E DEI BENI CULTURALI
03/B – INORGANICO, TECNOLOGICO		
	03/B1 – FONDAMENTI DELLE SCIENZE CHIMICHE E SISTEMI INORGANICI	CHI/03 – CHIMICA GENERALE ED INORGANICA
	03/B2 – FONDAMENTI CHIMICI DELLE TECNOLOGIE	CHIM/07 – FONDAMENTI CHIMICI DELLE TECNOLOGIE
03/C – ORGANICO INDUSTRIALE		
	03/C1 – CHIMICA ORGANICA	CHIM/06 – CHIMICA ORGANICA
	03/C2 – CHIMICA INDUSTRIALE	CHIM/04 – CHIMICA INDUSTRIALE CHIM/05 – SCIENZA E TECNOLOGIA DEI MATERIALI POLIMERICI
03/D – FARMACEUTICO, TECNOLOGICO, ALIMENTARE		
	03/D1 – CHIMICA E TECNOLOGIE FARMACEUTICHE,	CHIM/08 – CHIMICA FARMACEUTICA CHIM/10 – CHIMICA DEGLI ALIMENTI

	TOSSICOLOGICHE E NUTRACEUTICO-ALIMENTARI	CHIM/11 – CHIMICA E BIOTECNOLOGIA DELLE FERMENTAZIONI
	03/D2 – TECNOLOGIA SOCIOECONOMICA E NORMATIVA DEI MEDICINALI	CHIM/09 – FARMACEUTICO TECNOLOGICO APPLICATIVO

Livello 2: AREA - 05 - SCIENZE BIOLOGICHE

Livello 3	**Livello 4**	
Macrosettore Codice e Denominazione	**S.S.D. Codice e denominazione**	**VECCHIO S.S.D. Codice e Denominazione**
05/A - BIOLOGIA VEGETALE		
	05/A1 - BOTANICA	BIO/01 - BOTANICA GENERALE BIO/02 BOTANICA SISTEMATICA BIO/03 BOTANICA AMBIENTALE E APPLICATA
	05/A2 – FISIOLOGIA VEGETALE	BIO/04 - FISIOLOGIA VEGETALE
05/C – ECOLOGIA		
	05/C1 - ECOLOGIA	BIO/07 - ECOLOGIA
05/E - BIOCHIMICA E BIOLOGIA MOLECOLARE SPERIMENTALI E CLINICHE		
	05/E1- BIOCHIMICA GENERALE E BIOCHIMICA CLINICA (*)	BIO/10 – BIOCHIMICA
	05/E2 - BIOLOGIA MOLECOLARE (*)	BIO/11 - BIOLOGIA MOLECOLARE
05/I - GENETICA E MICROBIOLOGIA		
	05/I1- GENETICA E MICROBIOLOGIA	BIO/18 – GENETICA BIO/19 – MICROBIOLOGIA

Livello 2: AREA - 07 - SCIENZE AGRARIE E VETERINARIE

Livello 3	**Livello 4**	
Macrosettore Codice e Denominazione	**S.S.D. Codice e denominazione**	**VECCHIO S.S.D. Codice e Denominazione**
07/B – SISTEMI COLTURALI AGRARI E FORESTALI		
	07/B2 – SCIENZE E TECNOLOGIE DEI SISTEMI ARBOREI E FORESTALI	AGR/03 – ARBORICOLTURA GENERALE E COLTIVAZIONI ARBOREE
07/D – PATOLOGIA VEGETALE E ENTOMOLOGIA		
	07/D1 – PATOLOGIA VEGETALE E ENTOMOLOGIA	AGR/12 – PATOLOGIA VEGETALE
07/E – CHIMICA E GENETICA AGRARIA		
	07/E1 – CHIMICA E GENETICA AGRARIA	AGR/07 – GENETICA AGRARIA AGR/13 – CHIMICA AGRARIA AGR/14 – PEDOLOGIA
07/F – TECNOLOGIE ALIMENTARI E MICROBIOLOGIA AGRARIA		
	07/F1 – SCIENZE E TECNOLOGIE ALIMENTARI	AGR/15 – SCIENZE E TECNOLOGIE ALIMENTARI
	07/F2 – MICROBIOLOGIA AGRARIA	AGR/16 – MICROBIOLOGIA AGRARIA

Livello 2: AREA - 09 – INGEGNERIA INDUSTRIALE E DELL'INFORMAZIONE

Livello 3	**Livello 4**	
Macrosettore Codice e Denominazione	**S.S.D. Codice e denominazione**	**VECCHIO S.S.D. Codice e Denominazione**
09/D – INGEGNERIA CHIMICA E DEI MATERIALI		
	09/D3 – IMPIANTI E PROCESSI INDUSTRIALI CHIMICI	ING-IND/25 - IMPIANTI CHIMICI ING-IND/27 CHIMICA INDUSTRIALE E TECNOLOGICA

ALLEGATO B)

ARTE, ARCHEOLOGIA, STORIA, SOCIETA'

N.	COGNOME E NOME	RUOLO	SSD	
1	AIKEMA Bernard Jan Hendrik	Ordinario	L-ART/02	STORIA DELL'ARTE MODERNA
2	CASTAGNETTI Andrea	Ordinario	M-STO/01	STORIA MEDIEVALE
3	DI NICOLA Paola	Ordinario	SPS/08	SOCIOLOGIA DEI PROCESSI CULTURALI E COMUNICATIVI
4	FRANCO Tiziana	Ordinario	L-ART/01	STORIA DELL'ARTE MEDIEVALE
5	FRANZINA Emilio	Ordinario	M-STO/04	STORIA CONTEMPORANEA
6	MAHER Vanessa Anne	Ordinario	M-DEA/01	DISC. DEMOETNOANTROPOLOGICHE
7	MASTROCINQUE Attilio	Ordinario	L-ANT/03	STORIA ROMANA
8	OLIVATO Loredana	Ordinario	L-ART/02	STORIA DELL'ARTE MODERNA
9	PASTORE Alessandro	Ordinario	M-STO/02	STORIA MODERNA
10	PRANDI Luisa	Ordinario	L-ANT/02	STORIA GRECA
11	ROBIGLIO Claudia	Ordinario	M-GGR/01	GEOGRAFIA
12	ROMAGNANI Gian Paolo	Ordinario	M-STO/02	STORIA MODERNA
13	SALGARO Silvino	Ordinario	M-GGR/01	GEOGRAFIA
14	SANGUANINI Bruno	Ordinario	SPS/08	SOCIOLOGIA DEI PROCESSI CULTURALI E COMUNICATIVI
15	SECONDULFO Domenico	Ordinario	SPS/07	SOCIOLOGIA GENERALE
16	VANTINI Sandra	Ordinario	M-GGR/01	GEOGRAFIA
17	VARANINI Gian Maria	Ordinario	M-STO/01	STORIA MEDIEVALE
18	VECCHIATO Francesco	Ordinario	M-STO/04	STORIA CONTEMPORANEA
19	ARCANGELI Alessandro	Associato	M-STO/02	STORIA MODERNA
20	BASSO Patrizia	Associato	L-ANT/03	STORIA ROMANA
21	BUONOPANE Alfredo	Associato	L-ANT/03	STORIA ROMANA
22	CAMURRI Renato	Associato	M-STO/04	STORIA CONTEMPORANEA
23	CIANCIO Luca	Associato	M-STO/05	Storia delle scienze e delle tecniche
24	COCCHI Daniela	Associato	L-ANT/01	PREISTORIA E PROTOSTORIA
25	DAL POZZOLO Enrico	Associato	L-ART/02	STORIA DELL'ARTE MODERNA
26	FACCHINI Giuliana Maria	Associato	L-ANT/07	ARCHEOLOGIA CLASSICA
27	GAMBERONI Emanuela	Associato	M-GGR/01	GEOGRAFIA
28	GOLINELLI Paolo	Associato	M-STO/01	STORIA MEDIEVALE
29	NIERO Mauro	Associato	SPS/07	SOCIOLOGIA GENERALE
30	PAPPALARDO Maria Laura	Associato	M-GGR/01	GEOGRAFIA
31	PASINI Roberto	Associato	L-ART/03	STORIA DELL'ARTE CONTEMPORANEA
32	PONCHIA Simonetta	Associato	L-OR/01	STORIA DEL VICINO ORIENTE ANTICO
33	STANZANI Sandro	Associato	SPS/08	SOCIOLOGIA DEI PROCESSI CULTURALI E COMUNICATIVI
34	VOLPATO Giancarlo	Associato	M-STO/08	ARCHIVISTICA, BIBLIOGR., BIBLIOTECONOMIA
35	BARBIERATO Federico	Ricercatore	M-STO/02	STORIA MODERNA
36	BASSETTI Massimiliano	Ricercatore	M-STO/09	PALEOGRAFIA
37	CECCHI Sergio	Ricercatore	SPS/07	SOCIOLOGIA GENERALE
38	CODEN Fabio	Ricercatore	L-ART/01	STORIA DELL'ARTE MEDIEVALE
39	FORMIGA Federica	Ricercatore	M-STO/08	ARCHIVISTICA, BIBLIOGR., BIBLIOTECONOMIA
40	GARBELLOTTI Marina	Ricercatore	M-STO/02	STORIA MODERNA
41	GOSETTI Giorgio	Ricercatore	SPS/09	SOCIOLOGIA DEI PROCESSI ECONOMICI E DEL LAVORO
42	LANDUZZI Maria Gabriella	Ricercatore	SPS/08	SOCIOLOGIA DEI PROCESSI CULTURALI E COMUNICATIVI
43	LONARDI Cristina	Ricercatore	SPS/07	SOCIOLOGIA GENERALE
44	MARTINELLI Caterina	Ricercatore	M-GGR/01	GEOGRAFIA
45	MIGLIORATI Lorenzo	Ricercatore	SPS/08	SOCIOLOGIA DEI PROCESSI CULTURALI E COMUNICATIVI
46	MOLTENI Monica	Ricercatore	L-ART/04	MUSEOLOGIA E CRITICA ART. E DEL RESTAURO
47	MORANDI Emmanuele	Ricercatore	SPS/07	SOCIOLOGIA GENERALE
48	MORI Luca	Ricercatore	SPS/07	SOCIOLOGIA GENERALE
49	PAINI Anna Maria	Ricercatore	M-DEA/01	DISC. DEMOETNOANTROPOLOGICHE
50	ROSSI Mariaclara	Ricercatore	M-STO/07	STORIA DEL CRISTIANESIMO E DELLE CHIESE
51	SEVERI Rita	Ricercatore	L-LIN/10	LETTERATURA INGLESE
52	STOFFELLA Marco	Ricercatore	M-STO/01	STORIA MEDIEVALE
53	TEDOLDI Leonida	Ricercatore	SPS/03	STORIA DELLE ISTITUZIONI POLITICHE
54	TRONCA Luigi	Ricercatore	SPS/07	SOCIOLOGIA GENERALE
55	ZANGARINI Maurizio	Ricercatore	M-STO/04	STORIA CONTEMPORANEA
56	ZUMIANI Daniela	Ricercatore	ICAR/18	STORIA DELL'ARCHITETTURA

BIOTECNOLOGIE

N.	COGNOME E NOME	RUOLO	SSD	
1	BASSI Roberto	Ordinario	BIO/04	FISIOLOGIA VEGETALE
2	BETTINELLI Marco Giovanni	Ordinario	CHIM/03	CHIMICA GENERALE ED INORGANICA
3	BOSELLI Maurizio	Ordinario	AGR/03	ARBORICOLTURA GENERALE E COLTIVAZIONI ARBOREE
4	CECCHI Franco	Ordinario	ING-IND/25	IMPIANTI CHIMICI
5	DAL BELIN PERUFFO Angelo	Ordinario	AGR/15	SCIENZE E TECNOLOGIE ALIMENTARI
6	DOMINICI Paola	Ordinario	BIO/10	BIOCHIMICA
7	LEVI Marisa	Ordinario	BIO/01	BOTANICA GENERALE
8	MOLINARI Henriette	Ordinario	CHIM/06	CHIMICA ORGANICA
9	MONACO Ugo Luigi	Ordinario	BIO/11	BIOLOGIA MOLECOLARE
10	SPENA Angelo	Ordinario	AGR/07	GENETICA AGRARIA
11	TORRIANI Sandra	Ordinario	AGR/16	MICROBIOLOGIA AGRARIA
12	VALLINI Giovanni	Ordinario	AGR/16	MICROBIOLOGIA AGRARIA
13	VARANINI Zeno	Ordinario	AGR/13	CHIMICA AGRARIA
14	CRIMI Massimo	Associato	BIO/04	FISIOLOGIA VEGETALE
15	DELLEDONNE Massimo	Associato	AGR/07	GENETICA AGRARIA
16	FERRARINI Roberto	Associato	AGR/15	SCIENZE E TECNOLOGIE ALIMENTARI
17	FURINI Antonella	Associato	AGR/07	GENETICA AGRARIA
18	PEZZOTTI Mario	Associato	AGR/07	GENETICA AGRARIA
19	SPEGHINI Adolfo	Associato	CHIM/03	CHIMICA GENERALE ED INORGANICA
20	ASSFALG Michael	Ricercatore	CHIM/06	CHIMICA ORGANICA
21	BELLIN Diana	Ricercatore	AGR/07	GENETICA AGRARIA
22	BOLZONELLA David	Ricercatore	ING-IND/25	IMPIANTI CHIMICI
23	BOSSI Alessandra Maria	Ricercatore	BIO/10	BIOCHIMICA
24	CAPALDI Stefano	Ricercatore	BIO/11	BIOLOGIA MOLECOLARE
25	CECCONI Daniela	Ricercatore	CHIM/01	CHIMICA ANALITICA
26	CHIGNOLA Roberto	Ricercatore	MED/04	PATOLOGIA GENERALE
27	DALL'OSTO Luca	Ricercatore	BIO/04	FISIOLOGIA VEGETALE
28	FATONE Francesco	Ricercatore	ING-IND/25	IMPIANTI CHIMICI
29	GIORGETTI Alejandro	Ricercatore	BIO/10	BIOCHIMICA
30	GUANTIERI Valeria	Ricercatore	CHIM/06	CHIMICA ORGANICA
31	GUZZO Flavia	Ricercatore	BIO/01	BOTANICA GENERALE
32	LAMPIS Silvia	Ricercatore	BIO/19	MICROBIOLOGIA
33	MOLESINI Barbara	Ricercatore	BIO/04	FISIOLOGIA VEGETALE
34	PANDOLFINI Tiziana	Ricercatore	BIO/04	FISIOLOGIA VEGETALE
35	PERDUCA Massimiliano	Ricercatore	BIO/11	BIOLOGIA MOLECOLARE
36	PICCINELLI Fabio	Ricercatore	CHIM/03	CHIMICA GENERALE ED INORGANICA
37	POLVERARI Annalisa	Ricercatore	AGR/12	PATOLOGIA VEGETALE
38	RIZZI Corrado	Ricercatore	AGR/15	SCIENZE E TECNOLOGIE ALIMENTARI
39	SIMONATO Barbara	Ricercatore	AGR/15	SCIENZE E TECNOLOGIE ALIMENTARI
40	TORNIELLI Giovanni Battista	Ricercatore	AGR/03	ARBORICOLTURA GENERALE E COLTIVAZIONI ARBOREE
41	ZAPPAROLI Giacomo	Ricercatore	AGR/16	MICROBIOLOGIA AGRARIA
42	ZENONI Sara	Ricercatore	AGR/07	GENETICA AGRARIA
43	ZOCCATELLI Gianni	Ricercatore	CHIM/10	CHIMICA DEGLI ALIMENTI

CHIRURGIA

N.	COGNOME E NOME	RUOLO	SSD
1	ARTIBANI Walter	Ordinario	MED/24 UROLOGIA
2	BARTOLOZZI Pietro	Ordinario	MED/33 MALATTIE APPARATO LOCOMOTORE
3	BASSI Claudio	Ordinario	MED/18 CHIRURGIA GENERALE
4	CAVALLERI Giacomo	Ordinario	MED/28 MALATTIE ODONTOSTOMATOLOGICHE
5	COLLETTI Vittorio	Ordinario	MED/31 OTORINOLARINGOIATRIA
6	CORDIANO Claudio	Ordinario	MED/18 CHIRURGIA GENERALE
7	DE MANZONI Giovanni	Ordinario	MED/18 CHIRURGIA GENERALE
8	GUGLIELMI Alfredo	Ordinario	MED/18 CHIRURGIA GENERALE
9	LUZZANI Aldo	Ordinario	MED/41 ANESTESIOLOGIA
10	MAZZUCCO Alessandro	Ordinario	MED/23 CHIRURGIA CARDIACA
11	NOCINI Pier Francesco	Ordinario	MED/29 CHIRURGIA MAXILLOFACCIALE
12	OTTOLENGHI Alberto	Ordinario	MED/20 CHIRURGIA PEDIATRICA E INFANTILE
13	PEDERZOLI Paolo	Ordinario	MED/18 CHIRURGIA GENERALE
14	POLATI Enrico	Ordinario	MED/41 ANESTESIOLOGIA
15	BAGGIO Elda	Associato	MED/22 CHIRURGIA VASCOLARE
16	BERTOSSI Dario	Associato	MED/28 MALATTIE ODONTOSTOMATOLOGICHE
17	CAMOGLIO Francesco Saverio	Associato	MED/20 CHIRURGIA PEDIATRICA E INFANTILE
18	CANTATORE Giuseppe	Associato	MED/28 MALATTIE ODONTOSTOMATOLOGICHE
19	DE SANTIS Daniele	Associato	MED/28 MALATTIE ODONTOSTOMATOLOGICHE
20	FACCIONI Fiorenzo	Associato	MED/28 MALATTIE ODONTOSTOMATOLOGICHE
21	FAGGIAN Giuseppe	Associato	MED/23 CHIRURGIA CARDIACA
22	FENZI Alberto	Associato	FIS/07 FISICA APPLICATA (A BENI CULTURALI, AMBIENTALI, BIOLOGIA E MEDICINA)
23	GOTTIN Leonardo	Associato	MED/41 ANESTESIOLOGIA
24	IACONO Calogero	Associato	MED/18 CHIRURGIA GENERALE
25	LOMBARDO Giorgio	Associato	MED/28 MALATTIE ODONTOSTOMATOLOGICHE
26	LUCIANI Giovanni Battista	Associato	MED/23 CHIRURGIA CARDIACA
27	MALCHIODI Luciano	Associato	MED/28 MALATTIE ODONTOSTOMATOLOGICHE
28	MOTTA Antonio	Associato	MED/23 CHIRURGIA CARDIACA
29	POLLINI Giovanni Paolo	Associato	MED/18 CHIRURGIA GENERALE
30	RICCI Matteo	Associato	MED/33 MALATTIE APPARATO LOCOMOTORE
31	SANTINI Francesco	Associato	MED/23 CHIRURGIA CARDIACA
32	ALBANESE Massimo	Ricercatore	MED/28 MALATTIE ODONTOSTOMATOLOGICHE
33	ARAGNO Anna Maria Rosa	Ricercatore	MED/31 OTORINOLARINGOIATRIA
34	BARTOLONI Alberto	Ricercatore	MED/41 ANESTESIOLOGIA
35	BEDOGNI Alberto	Ricercatore	MED/29 CHIRURGIA MAXILLOFACCIALE
36	BERTOLINI Paolo	Ricercatore	MED/23 CHIRURGIA CARDIACA
37	BIANCHI Benedetta	Ricercatore	MED/41 ANESTESIOLOGIA
38	BORZELLINO Giuseppe	Ricercatore	MED/18 CHIRURGIA GENERALE
39	CERRUTO Maria Angela	Ricercatore	MED/24 UROLOGIA
40	COLLETTI Liliana	Ricercatore	MED/50 SCIENZE TECNICHE MEDICHE APPLICATE
41	D'AGOSTINO Antonio	Ricercatore	MED/28 MALATTIE ODONTOSTOMATOLOGICHE
42	DALL'OCA Carlo	Ricercatore	MED/33 MALATTIE APPARATO LOCOMOTORE
43	FALCONI Massimo	Ricercatore	MED/18 CHIRURGIA GENERALE
44	FERRARI Francesca	Ricercatore	MED/28 MALATTIE ODONTOSTOMATOLOGICHE
45	FRACASTORO Gerolamo	Ricercatore	MED/18 CHIRURGIA GENERALE
46	GIACOMELLO Luca	Ricercatore	MED/20 CHIRURGIA PEDIATRICA E INFANTILE
47	LOLLI Paola	Ricercatore	MED/18 CHIRURGIA GENERALE
48	MANGIANTE Gerardo	Ricercatore	MED/18 CHIRURGIA GENERALE
49	MARCHIORI Luigi	Ricercatore	MED/18 CHIRURGIA GENERALE
50	MAZZILLI Giulio	Ricercatore	MED/22 CHIRURGIA VASCOLARE
51	MILANO Aldo Domenico	Ricercatore	MED/23 CHIRURGIA CARDIACA
52	MONTRESOR Ettore	Ricercatore	MED/21 CHIRURGIA TORACICA
53	RUNGATSCHER Alessio	Ricercatore	MED/23 CHIRURGIA CARDIACA
54	SACCHETTO Luca	Ricercatore	MED/31 OTORINOLARINGOIATRIA
55	SCHWEIGER Vittorio	Ricercatore	MED/41 ANESTESIOLOGIA
56	SCURO Alberto	Ricercatore	MED/22 CHIRURGIA VASCOLARE
57	TREVISIOL Lorenzo	Ricercatore	MED/28 MALATTIE ODONTOSTOMATOLOGICHE
58	VECCHINI Eugenio	Ricercatore	MED/33 MALATTIE APPARATO LOCOMOTORE

ECONOMIA AZIENDALE

N.	COGNOME E NOME	RUOLO	SSD	
1	BACCARANI Claudio	Ordinario	SECS-P/08	ECONOMIA E GESTIONE DELLE IMPRESE
2	BEGALLI Diego	Ordinario	AGR/01	ECONOMIA ED ESTIMO RURALE
3	BERETTA ZANONI Andrea	Ordinario	SECS-P/07	ECONOMIA AZIENDALE
4	BORGHESI Antonio	Ordinario	SECS-P/08	ECONOMIA E GESTIONE DELLE IMPRESE
5	BOTTIGLIA Roberto	Ordinario	SECS-P/11	ECONOMIA DEGLI INTERMEDIARI FINANZIARI
6	BROGLIA Angela	Ordinario	SECS-P/07	ECONOMIA AZIENDALE
7	BRUNETTI Federico	Ordinario	SECS-P/08	ECONOMIA E GESTIONE DELLE IMPRESE
8	CAMPEDELLI Bettina	Ordinario	SECS-P/07	ECONOMIA AZIENDALE
9	CARLUCCIO Emanuele Maria	Ordinario	SECS-P/11	ECONOMIA DEGLI INTERMEDIARI FINANZIARI
10	CERIANI Giuseppe	Ordinario	SECS-P/07	ECONOMIA AZIENDALE
11	FAVRETTO Giuseppe	Ordinario	SECS-P/10	ORGANIZZAZIONE AZIENDALE
12	LAI Alessandro	Ordinario	SECS-P/07	ECONOMIA AZIENDALE
13	MARANGONI Giandemetrio	Ordinario	SECS-P/01	ECONOMIA POLITICA
14	RUTIGLIANO Michele	Ordinario	SECS-P/11	ECONOMIA DEGLI INTERMEDIARI FINANZIARI
15	TESSITORE Antonio	Ordinario	SECS-P/07	ECONOMIA AZIENDALE
16	TESTA Federico	Ordinario	SECS-P/08	ECONOMIA E GESTIONE DELLE IMPRESE
17	UGOLINI Marta Maria	Ordinario	SECS-P/08	ECONOMIA E GESTIONE DELLE IMPRESE
18	CAPITELLO Roberta	Associato	AGR/01	ECONOMIA ED ESTIMO RURALE
19	CHESINI Giuseppina	Associato	SECS-P/11	ECONOMIA DEGLI INTERMEDIARI FINANZIARI
20	CORBELLA Silvano	Associato	SECS-P/07	ECONOMIA AZIENDALE
21	CORSI Corrado	Associato	SECS-P/07	ECONOMIA AZIENDALE
22	GIARETTA Elena	Associato	SECS-P/08	ECONOMIA E GESTIONE DELLE IMPRESE
23	GOLDONI Giovanni	Associato	SECS-P/13	SCIENZE MERCEOLOGICHE
24	LEARDINI Chiara	Associato	SECS-P/07	ECONOMIA AZIENDALE
25	LIONZO Andrea	Associato	SECS-P/07	ECONOMIA AZIENDALE
26	PICHLER Flavio	Associato	SECS-P/11	ECONOMIA DEGLI INTERMEDIARI FINANZIARI
27	ROFFIA Paolo	Associato	SECS-P/07	ECONOMIA AZIENDALE
28	ROSSIGNOLI Cecilia	Associato	SECS-P/10	ORGANIZZAZIONE AZIENDALE
29	SIGNORI Paola	Associato	SECS-P/08	ECONOMIA E GESTIONE DELLE IMPRESE
30	BONFANTI Angelo	Ricercatore	SECS-P/08	ECONOMIA E GESTIONE DELLE IMPRESE
31	CANTELE Silvia	Ricercatore	SECS-P/07	ECONOMIA AZIENDALE
32	CASTELLANI Paola	Ricercatore	SECS-P/08	ECONOMIA E GESTIONE DELLE IMPRESE
33	CUBICO Serena	Ricercatore	M-PSI/06	Psicologia del lavoro e delle organizzazioni
34	DE CRESCENZO Veronica	Ricercatore	SECS-P/11	ECONOMIA DEGLI INTERMEDIARI FINANZIARI
35	FACCINCANI Lorenzo	Ricercatore	SECS-P/11	ECONOMIA DEGLI INTERMEDIARI FINANZIARI
36	FARINON Paolo	Ricercatore	SECS-P/07	ECONOMIA AZIENDALE
37	FLORIO Cristina	Ricercatore	SECS-P/07	ECONOMIA AZIENDALE
38	GAETA Davide Nicola Vincenzo	Ricercatore	AGR/01	ECONOMIA ED ESTIMO RURALE
39	GAUDENZI Barbara	Ricercatore	SECS-P/08	ECONOMIA E GESTIONE DELLE IMPRESE
40	GUERRINI Andrea	Ricercatore	SECS-P/07	ECONOMIA AZIENDALE
41	LASSINI Ugo	Ricercatore	SECS-P/07	ECONOMIA AZIENDALE
42	MION Giorgio	Ricercatore	SECS-P/07	ECONOMIA AZIENDALE
43	MOLA Lapo	Ricercatore	SECS-P/10	ORGANIZZAZIONE AZIENDALE
44	ROSSATO Chiara	Ricercatore	SECS-P/08	ECONOMIA E GESTIONE DELLE IMPRESE
45	RUSSO Ivan	Ricercatore	SECS-P/07	ECONOMIA AZIENDALE
46	SIMEONI Francesca	Ricercatore	SECS-P/08	ECONOMIA E GESTIONE DELLE IMPRESE
47	STACCHEZZINI Riccardo	Ricercatore	SECS-P/07	ECONOMIA AZIENDALE
48	VERNIZZI Silvia	Ricercatore	SECS-P/07	ECONOMIA AZIENDALE
49	VIGOLO Vania	Ricercatore	SECS-P/08	ECONOMIA E GESTIONE DELLE IMPRESE

FILOLOGIA, LETTERATURE E LINGUISTICA

N.	COGNOME E NOME	RUOLO	SSD	
1	AVEZZU' Guido	Ordinario	L-FIL-LET/02	LINGUA E LETT. GRECA
2	BABBI Anna Maria	Ordinario	L-FIL-LET/09	FILOLOGIA E LINGUISTICA ROMANZA
3	BERTAZZOLI Raffaella	Ordinario	L-FIL-LET/14	CRITICA LETTERARIA E LETTERATURE COMPARATE
4	BETTONI Camilla	Ordinario	L-LIN/02	DIDATTICA DELLE LINGUE MODERNE
5	BOTTARI Guglielmo	Ordinario	L-FIL-LET/13	FILOLOGIA DELLA LETTERATURA ITALIANA
6	CAVARZERE Alberto	Ordinario	L-FIL-LET/04	LINGUA E LETT. LATINA
7	DELFITTO Denis	Ordinario	L-LIN/01	GLOTTOLOGIA E LINGUISTICA
8	DONADI Francesco	Ordinario	L-FIL-LET/05	FILOLOGIA CLASSICA
9	EBANI Nadia	Ordinario	L-FIL-LET/10	LETTERATURA ITALIANA
10	GRAFFI Giorgio	Ordinario	L-LIN/01	GLOTTOLOGIA E LINGUISTICA
11	LESO Erasmo	Ordinario	L-FIL-LET/12	LINGUISTICA ITALIANA
12	LONARDI Gilberto	Ordinario	L-FIL-LET/10	LETTERATURA ITALIANA
13	LONGHI Silvia	Ordinario	L-FIL-LET/10	LETTERATURA ITALIANA
14	MARCHI Gian Paolo	Ordinario	L-FIL-LET/10	LETTERATURA ITALIANA
15	RICOTTILLI Licinia Maria	Ordinario	L-FIL-LET/04	LINGUA E LETT. LATINA
16	TANI Stefano	Ordinario	L-FIL-LET/14	CRITICA LETTERARIA E LETTERATURE COMPARATE
17	ALLEGRI Mario	Associato	L-FIL-LET/11	LETTERATURA ITALIANA CONTEMPOR.
18	BRUSEGAN Rosanna	Associato	L-FIL-LET/09	FILOLOGIA E LINGUISTICA ROMANZA
19	CHIECCHI Giuseppe	Associato	L-FIL-LET/01	CIVILTÀ EGEE
20	COTTICELLI Paola	Associato	L-LIN/01	GLOTTOLOGIA E LINGUISTICA
21	DE PRISCO Antonio	Associato	L-FIL-LET/08	LETTERATURA LATINA MEDIEVALE E UMANISTICA
22	GIRARDI Antonio	Associato	L-FIL-LET/12	LINGUISTICA ITALIANA
23	GROSSATO Elisa	Associato	L-ART/07	MUSICOLOGIA E STORIA MUSICA
24	REGGIANI Renato	Associato	L-FIL-LET/04	LINGUA E LETT. LATINA
25	VIOLA Corrado	Associato	L-FIL-LET/10	LETTERATURA ITALIANA
26	ZACCARELLO Michelangelo	Associato	L-FIL-LET/13	FILOLOGIA DELLA LETTERATURA ITALIANA
27	BARTOLUCCI Lidia	Ricercatore	L-FIL-LET/09	FILOLOGIA E LINGUISTICA ROMANZA
28	BORGHETTI Vincenzo	Ricercatore	L-ART/07	MUSICOLOGIA E STORIA MUSICA
29	BRUNETTI Simona	Ricercatore	L-ART/05	DISCIPLINE DELLO SPETTACOLO
30	DANELONI Alessandro	Ricercatore	L-FIL-LET/13	FILOLOGIA DELLA LETTERATURA ITALIANA
31	FERRARINI Edoardo	Ricercatore	L-FIL-LET/08	LETTERATURA LATINA MEDIEVALE E UMANISTICA
32	FLAIM Carmen	Ricercatore	L-LIN/13	LETTERATURA TEDESCA
33	FORNER Fabio	Ricercatore	L-FIL-LET/10	LETTERATURA ITALIANA
34	LA TORRE Anna Maria	Ricercatore	L-ART/05	DISCIPLINE DELLO SPETTACOLO
35	MELLONI Chiara	Ricercatore	L-LIN/01	GLOTTOLOGIA E LINGUISTICA
36	PAGLIAROLI Stefano	Ricercatore	L-FIL-LET/13	FILOLOGIA DELLA LETTERATURA ITALIANA
37	PASQUALICCHIO Nicola	Ricercatore	L-ART/05	DISCIPLINE DELLO SPETTACOLO
38	PELLEGRINI Paolo	Ricercatore	L-FIL-LET/13	FILOLOGIA DELLA LETTERATURA ITALIANA
39	RODIGHIERO Andrea	Ricercatore	L-FIL-LET/02	LINGUA E LETT. GRECA
40	ROSSETTI Maria Gabriella	Ricercatore	L-FIL-LET/04	LINGUA E LETT. LATINA
41	SANDRINI Giuseppe	Ricercatore	L-FIL-LET/10	LETTERATURA ITALIANA
42	SCANDOLA Alberto	Ricercatore	L-ART/06	CINEMA, FOTOGRAFIA E TELEVISIONE
43	SCATTOLIN Paolo	Ricercatore	L-FIL-LET/02	LINGUA E LETT. GRECA
44	SCHIAVO Piera	Ricercatore	L-FIL-LET/10	LETTERATURA ITALIANA
45	SOLDANI Arnaldo	Ricercatore	L-FIL-LET/12	LINGUISTICA ITALIANA
46	PRUGNI Gianmario	Assistente	L-FIL-LET/04	LINGUA E LETT. LATINA

FILOSOFIA, PEDAGOGIA E PSICOLOGIA

N.	COGNOME E NOME	RUOLO	SSD	
1	BELLOTTO Massimo	Ordinario	M-PSI/06	Psicologia del lavoro e delle organizzazion
2	CAVARERO Adriana	Ordinario	SPS/01	Filosofia politica
3	DE BERNARDI Bianca	Ordinario	M-PSI/04	Psicologia dello sviluppo e dell'educazione
4	FILIPPI Natale	Ordinario	M/PED-01	Pedagogia generale e sociale
5	LAROCCA Francesco	Ordinario	M/PED-03	Didattica e Pedagogia Speciale
6	LOMBARDO Mario	Ordinario	M-FIL/01	Filosofia teoretica
7	LONGO Mario	Ordinario	M-FIL/06	Storia della filosofia
8	MARCOLUNGO Ferdinando	Ordinario	M-FIL/01	Filosofia teoretica
9	MARTINI Massimo	Ordinario	M-PSI/05	Psicologia sociale
10	MORETTO Antonio	Ordinario	M-FIL/01	Filosofia teoretica
11	MORTARI Luigina	Ordinario	M/PED-01	Pedagogia generale e sociale
12	PIASERE Leonardo	Ordinario	M-DEA/01	DISC. DEMOETNOANTROPOLOGICHE
13	PIUSSI Anna Maria	Ordinario	M/PED-01	Pedagogia generale e sociale
14	PORTERA Agostino	Ordinario	M/PED-01	Pedagogia generale e sociale
15	POZZO Riccardo	Ordinario	M-FIL/06	Storia della filosofia
16	SAVARDI Ugo	Ordinario	M-PSI/01	Psicologia generale
17	SCIUTO Italo	Ordinario	M-FIL/03	Filosofia morale
18	AGOSTI Alberto	Associato	M/PED-03	Didattica e Pedagogia Speciale
19	BATTISTELLI Adalgisa	Associato	M-PSI/06	Psicologia del lavoro e delle organizzazion
20	CAPILUPPI Claudio	Associato	SECS-S/05	STATISTICA SOCIALE
21	CAROZZI Pier Angelo	Associato	M-STO/06	STORIA DELLE RELIGIONI
22	GAMBAZZI Paolo	Associato	M-FIL/04	Estetica
23	GECCHELE Mario	Associato	M/PED-02	Storia della pedagogia
24	NAPOLITANO Linda	Associato	M-FIL/07	Storia della filosofia antica
25	PANATTONI Riccardo	Associato	M-FIL/03	Filosofia morale
26	PASINI Margherita	Associato	M-PSI/03	Psicometria
27	PEDRAZZA Monica	Associato	M-PSI/05	Psicologia sociale
28	PERUZZI Enrico	Associato	M-FIL/06	Storia della filosofia
29	SALA Gabriel Maria	Associato	M/PED-01	Pedagogia generale e sociale
30	TOMMASI Wanda	Associato	M-FIL/06	Storia della filosofia
31	ZAMBONI Chiara	Associato	M-FIL/01	Filosofia teoretica
32	BARBETTA Maria Cecilia	Ricercatore	M-FIL/06	Storia della filosofia
33	BERNINI Lorenzo	Ricercatore	SPS/01	Filosofia politica
34	BLEZZA Silvia	Ricercatore	M/PED-01	Pedagogia generale e sociale
35	BURRO Roberto	Ricercatore	M-PSI/01	Psicologia generale
36	CIMA Rosanna	Ricercatore	M/PED-01	PEDAGOGIA GENERALE E SOCIALE
37	CUSINATO Guido	Ricercatore	M-FIL/03	Filosofia morale
38	DAL TOSO Paola	Ricercatore	M/PED-02	Storia della pedagogia
39	DE CORDOVA Federica	Ricercatore	M-PSI/05	Psicologia sociale
40	DE VITA Antonietta	Ricercatore	M/PED-01	Pedagogia generale e sociale
41	DUSI Paola	Ricercatore	M/PED-01	Pedagogia generale e sociale
42	ERLE Giorgio	Ricercatore	M-FIL/03	Filosofia morale
43	FRANCK Giorgio	Ricercatore	M-FIL/04	Estetica
44	GIRELLI Claudio	Ricercatore	M/PED-04	Pedagogia sperimentale
45	GIUSPOLI Paolo	Ricercatore	M-FIL/01	Filosofia teoretica
46	GUARALDO Olivia	Ricercatore	SPS/01	Filosofia politica
47	LASCIOLI Angelo	Ricercatore	M/PED-03	Didattica e Pedagogia Speciale
48	LAVELLI Manuela	Ricercatore	M-PSI/04	Psicologia dello sviluppo e dell'educazione
49	LORO Daniele	Ricercatore	M/PED-01	Pedagogia generale e sociale
50	MENEGHINI Anna Maria	Ricercatore	M-PSI/07	PSICOLOGIA DINAMICA
51	MESSETTI Giuseppina	Ricercatore	M/PED-03	Didattica e Pedagogia Speciale
52	MORO Valentina	Ricercatore	M-PSI/02	Psicobiologia e Psicologia fisiologica
53	POGGI Davide	Ricercatore	M-FIL/01	Filosofia teoretica
54	PROCURANTI Lucia	Ricercatore	M-FIL/06	Storia della filosofia
55	RACCANELLO Daniela	Ricercatore	M-PSI/04	Psicologia dello sviluppo e dell'educazione
56	RAPPAGLIOSI Cristina Maria	Ricercatore	M-PSI/06	Psicologia del lavoro e delle organizzazion
57	SARTORI Riccardo	Ricercatore	M-PSI/03	Psicometria
58	SITA' Chiara	Ricercatore	M/PED-01	Pedagogia generale e sociale
59	SOLLA Gianluca	Ricercatore	M-FIL/01	Filosofia teoretica
60	TACCONI Giuseppe	Ricercatore	M/PED-03	Didattica e Pedagogia Speciale
61	TUPPINI Tommaso	Ricercatore	M-FIL/06	Storia della filosofia

INFORMATICA

N.	COGNOME E NOME	RUOLO	SSD	
1	BONACINA Maria Paola	Ordinario	INF/01	INFORMATICA
2	BOS Leonard Peter	Ordinario	MAT/08	ANALISI NUMERICA
3	COMBI Carlo	Ordinario	INF/01	INFORMATICA
4	DALLACASA Valerio	Ordinario	FIS/07	FISICA APPLICATA (A BENI CULTURALI, AMBIENTALI, BIOLOGIA E MEDICINA)
5	FERRO Ruggero	Ordinario	MAT/01	LOGICA MATEMATICA
6	FUMMI Franco	Ordinario	ING-INF/05	SISTEMI DI ELABORAZIONE DELLE INFORMAZIONI
7	GIACOBAZZI Roberto	Ordinario	INF/01	INFORMATICA
8	MANCA Vincenzo	Ordinario	INF/01	INFORMATICA
9	MARIOTTO Gino	Ordinario	FIS/01	FISICA SPERIMENTALE
10	MASINI Andrea	Ordinario	INF/01	INFORMATICA
11	MORATO Laura Maria	Ordinario	MAT/06	PROBABILITÀ E STATISTICA MATEMATICA
12	MURINO Vittorio	Ordinario	INF/01	INFORMATICA
13	SEGALA Roberto	Ordinario	INF/01	INFORMATICA
14	VILLA Tiziano	Ordinario	ING-INF/05	SISTEMI DI ELABORAZIONE DELLE INFORMAZIONI
15	ZAMPIERI Gaetano	Ordinario	MAT/05	ANALISI MATEMATICA
16	ANGELERI Lidia	Associato	MAT/02	ALGEBRA
17	BALDO Sisto	Associato	MAT/05	ANALISI MATEMATICA
18	BELUSSI Alberto	Associato	ING-INF/05	SISTEMI DI ELABORAZIONE DELLE INFORMAZIONI
19	FIORINI Paolo	Associato	ING-INF/04	AUTOMATICA
20	FUSIELLO Andrea	Associato	INF/01	INFORMATICA
21	GIACHETTI Andrea	Associato	INF/01	INFORMATICA
22	GREGORIO Enrico	Associato	MAT/02	ALGEBRA
23	MENEGAZ Gloria	Associato	INF/01	INFORMATICA
24	MERRO Massimo	Associato	INF/01	INFORMATICA
25	MONTI Francesca	Associato	FIS/01	FISICA SPERIMENTALE
26	ORLANDI Giandomenico	Associato	MAT/05	ANALISI MATEMATICA
27	PICA Angelo	Associato	MAT/08	ANALISI NUMERICA
28	SPERA Mauro	Associato	MAT/03	GEOMETRIA
29	SPOTO Nicola Fausto	Associato	INF/01	INFORMATICA
30	VIGANO' Luca	Associato	INF/01	INFORMATICA
31	BELLIN Gianluigi	Ricercatore	MAT/01	LOGICA MATEMATICA
32	BICEGO Manuele	Ricercatore	ING-INF/05	SISTEMI DI ELABORAZIONE DELLE INFORMAZIONI
33	BOMBIERI Nicola	Ricercatore	ING-INF/05	SISTEMI DI ELABORAZIONE DELLE INFORMAZIONI
34	CALIARI Marco	Ricercatore	MAT/08	ANALISI NUMERICA
35	CARRA Damiano	Ricercatore	ING-INF/05	SISTEMI DI ELABORAZIONE DELLE INFORMAZIONI
36	CASTELLANI Umberto	Ricercatore	INF/01	INFORMATICA
37	CRISTANI Marco	Ricercatore	INF/01	INFORMATICA
38	CRISTANI Matteo	Ricercatore	INF/01	INFORMATICA
39	DI PIERRO Alessandra	Ricercatore	INF/01	INFORMATICA
40	FARINELLI Alessandro	Ricercatore	INF/01	INFORMATICA
41	FRANCO Giuditta	Ricercatore	INF/01	INFORMATICA
42	MANTESE Francesca	Ricercatore	MAT/02	ALGEBRA
43	MARIGONDA Antonio	Ricercatore	MAT/05	ANALISI MATEMATICA
44	MARZOLA Pasquina	Ricercatore	FIS/07	FISICA APPLICATA (A BENI CULTURALI, AMBIENTALI, BIOLOGIA E MEDICINA)
45	MASTROENI Isabella	Ricercatore	INF/01	INFORMATICA
46	OLIBONI Barbara	Ricercatore	INF/01	INFORMATICA
47	POSENATO Roberto	Ricercatore	INF/01	INFORMATICA
48	PRAVADELLI Graziano	Ricercatore	ING-INF/05	SISTEMI DI ELABORAZIONE DELLE INFORMAZIONI
49	QUAGLIA Davide	Ricercatore	ING-INF/05	SISTEMI DI ELABORAZIONE DELLE INFORMAZIONI
50	ROMEO Alessandro	Ricercatore	FIS/07	FISICA APPLICATA (A BENI CULTURALI, AMBIENTALI, BIOLOGIA E MEDICINA)
51	SOLITRO Ugo	Ricercatore	INF/01	INFORMATICA
52	SQUASSINA Marco	Ricercatore	MAT/05	ANALISI MATEMATICA

LINGUE E LETTERATURE STRANIERE

N.	COGNOME E NOME	RUOLO	SSD	
1	BIGLIAZZI Silvia	Ordinario	L-LIN/10	LETTERATURA INGLESE
2	BOGNOLO Anna	Ordinario	L-LIN/05	LETTERATURA SPAGNOLA
3	BONAZZA Sergio	Ordinario	L-LIN/21	SLAVISTICA
4	BUSCH BERNARD Walter	Ordinario	L-LIN/13	LETTERATURA TEDESCA
5	CARPI Daniela	Ordinario	L-LIN/10	LETTERATURA INGLESE
6	CIPOLLA Maria Adele	Ordinario	L-FIL-LET/15	FILOLOGIA GERMANICA
7	FACCHINETTI Roberta	Ordinario	L-LIN/12	LINGUA E TRADUZIONE – LINGUA INGLESE
8	GAGLIARDI Cesare	Ordinario	L-LIN/12	LINGUA E TRADUZIONE – LINGUA INGLESE
9	GORRIS Rosanna	Ordinario	L-LIN/03	LETTERATURA FRANCESE
10	MASSARIELLO Giovanna	Ordinario	L-LIN/01	GLOTTOLOGIA E LINGUISTICA
11	MONTI Silvia	Ordinario	L-LIN/05	LETTERATURA SPAGNOLA
12	PIVA Franco	Ordinario	L-LIN/03	LETTERATURA FRANCESE
13	SCHIFFERMULLER Isolde	Ordinario	L-LIN/13	LETTERATURA TEDESCA
14	TAROZZI Bianca Grazia	Ordinario	L-LIN/11	LINGUE E LETTERATURE ANGLOAMERICANE
15	TOMASELLI Alessandra	Ordinario	L-LIN/14	LINGUA E TRADUZIONE – LINGUA TEDESCA
16	ALBER Birgit	Associato	L-LIN/14	LINGUA E TRADUZIONE – LINGUA TEDESCA
17	AMBROSI Paola	Associato	L-LIN/05	LETTERATURA SPAGNOLA
18	BEZRUCKA Yvonne	Associato	L-LIN/10	LETTERATURA INGLESE
19	CAGLIERO Roberto	Associato	L-LIN/12	LINGUA E TRADUZIONE – LINGUA INGLESE
20	DAL CORSO Mario	Associato	L-LIN/03	LETTERATURA FRANCESE
21	DE LOTTO Cinzia	Associato	L-LIN/21	SLAVISTICA
22	FOSSALUZZA Giorgio	Associato	L-ART/02	STORIA DELL'ARTE MODERNA
23	GENETTI Stefano	Associato	L-LIN/03	LETTERATURA FRANCESE
24	GRANA Maria	Associato	L-LIN/06	LINGUA E LETTERATURE ISPANOAMERICANE
25	KOFLER Peter Erwin	Associato	L-LIN/13	LETTERATURA TEDESCA
26	LIGAS Pierluigi	Associato	L-LIN/04	LINGUA E TRADUZIONE –LINGUA FRANCESE
27	LOCHER Elmar	Associato	L-LIN/13	LETTERATURA TEDESCA
28	NAVARRO Maria Del Carmen	Associato	L-LIN/07	LINGUA E TRADUZIONE – LINGUA SPAGNOLA
29	PESCATORI Sergio	Associato	L-LIN/21	SLAVISTICA
30	RABANUS Stefan	Associato	L-LIN/14	LINGUA E TRADUZIONE – LINGUA TEDESCA
31	SASSI Carla	Associato	L-LIN/10	LETTERATURA INGLESE
32	STORARI Gilberto	Associato	L-LIN/12	LINGUA E TRADUZIONE – LINGUA INGLESE
33	ZINATO Andrea	Associato	L-LIN/05	LETTERATURA SPAGNOLA
34	ZINATO Susanna	Associato	L-LIN/10	LETTERATURA INGLESE
35	ALOE Stefano	Ricercatore	L-LIN/21	SLAVISTICA
36	BATTISTI Chiara	Ricercatore	L-LIN/10	LETTERATURA INGLESE
37	CALVI Lisanna	Ricercatore	L-LIN/10	LETTERATURA INGLESE
38	CANTARINI Sibilla	Ricercatore	L-LIN/14	LINGUA E TRADUZIONE – LINGUA TEDESCA
39	COLOMBO Laura Maria	Ricercatore	L-LIN/03	LETTERATURA FRANCESE
40	DAL MASO Serena	Ricercatore	L-LIN/01	GLOTTOLOGIA E LINGUISTICA
41	DALLE PEZZE Francesca	Ricercatore	L-LIN/07	LINGUA E TRADUZIONE – LINGUA SPAGNOLA
42	DEGANI Marta	Ricercatore	L-LIN/12	LINGUA E TRADUZIONE – LINGUA INGLESE
43	FIORATO Sidia	Ricercatore	L-LIN/10	LETTERATURA INGLESE
44	FRASSI Paolo	Ricercatore	L-LIN/04	LINGUA E TRADUZIONE –LINGUA FRANCESE
45	GALLO Antonella	Ricercatore	L-LIN/05	LETTERATURA SPAGNOLA
46	GAMBIN Felice	Ricercatore	L-LIN/05	LETTERATURA SPAGNOLA
47	LARCATI Arturo	Ricercatore	L-LIN/13	LETTERATURA TEDESCA
48	LORENZETTI Maria Ivana	Ricercatore	L-LIN/12	LINGUA E TRADUZIONE – LINGUA INGLESE
49	MIOTTI Renzo	Ricercatore	L-LIN/07	LINGUA E TRADUZIONE – LINGUA SPAGNOLA
50	NERI Stefano	Ricercatore	L-LIN/05	LETTERATURA SPAGNOLA
51	PERAZZOLO Paola	Ricercatore	L-LIN/03	LETTERATURA FRANCESE
52	PES Annalisa	Ricercatore	L-LIN/10	LETTERATURA INGLESE
53	RODRIGUEZ ABELLA Rosa Maria	Ricercatore	L-LIN/07	LINGUA E TRADUZIONE – LINGUA SPAGNOLA
54	SALGARO Massimo	Ricercatore	L-LIN/13	LETTERATURA TEDESCA
55	SIEDINA Giovanna	Ricercatore	L-LIN/21	SLAVISTICA
56	VETTOREL Paola	Ricercatore	L-LIN/12	LINGUA E TRADUZIONE – LINGUA INGLESE
57	ZANFEI Anna	Ricercatore	L-LIN/12	LINGUA E TRADUZIONE – LINGUA INGLESE

MEDICINA

N.	COGNOME E NOME	RUOLO	SSD
1	ADAMI Silvano	Ordinario	MED/16 REUMATOLOGIA
2	BAMBARA Lisa Maria	Ordinario	MED/16 REUMATOLOGIA
3	BONORA Enzo	Ordinario	MED/13 ENDOCRINOLOGIA
4	CETTO Gianluigi	Ordinario	MED/06 ONCOLOGIA MEDICA
5	COMINACINI Luciano	Ordinario	MED/09 MEDICINA INTERNA
6	GIROLOMONI Giampiero	Ordinario	MED/35 MALATTIE CUTANEE E VENEREE
7	LECHI Alessandro	Ordinario	MED/09 MEDICINA INTERNA
8	LUPO Antonio	Ordinario	MED/14 NEFROLOGIA
9	OLIVIERI Oliviero	Ordinario	MED/09 MEDICINA INTERNA
10	PIZZOLO Giovanni	Ordinario	MED/15 MALATTIE DEL SANGUE
11	VANTINI Italo	Ordinario	MED/12 GASTROENTEROLOGIA
12	VASSANELLI Corrado	Ordinario	MED/11 MALATTIE DELL'APPARATO CARDIO VASCOLARE
13	AMBROSETTI Achille	Associato	MED/15 MALATTIE DEL SANGUE
14	AROSIO Enrico	Associato	MED/09 MEDICINA INTERNA
15	BENINI Luigi	Associato	MED/12 GASTROENTEROLOGIA
16	BONADONNA Riccardo	Associato	MED/13 ENDOCRINOLOGIA
17	DE FRANCESCHI Lucia	Associato	MED/09 MEDICINA INTERNA
18	FATTOVICH Giovanna	Associato	MED/09 MEDICINA INTERNA
19	FERRARI Marcello	Associato	MED/10 MALATTIE DELL'APPARATO RESPIRATORIO
20	FRULLONI Luca	Associato	MED/12 GASTROENTEROLOGIA
21	GIRELLI Domenico	Associato	MED/09 MEDICINA INTERNA
22	LUNARDI Claudio	Associato	MED/09 MEDICINA INTERNA
23	MINUZ Pietro	Associato	MED/09 MEDICINA INTERNA
24	MOGHETTI Paolo	Associato	MED/13 ENDOCRINOLOGIA
25	RIBICHINI Flavio Luciano	Associato	MED/11 MALATTIE DELL'APPARATO CARDIO VASCOLARE
26	TODESCHINI Giuseppe	Associato	MED/15 MALATTIE DEL SANGUE
27	VINANTE Fabrizio	Associato	MED/15 MALATTIE DEL SANGUE
28	ZAMBONI Mauro	Associato	MED/09 MEDICINA INTERNA
29	ABATERUSSO Cataldo	Ricercatore	MED/14 NEFROLOGIA
30	BENINI Franco	Ricercatore	MED/09 MEDICINA INTERNA
31	BERTOLDO Francesco	Ricercatore	MED/09 MEDICINA INTERNA
32	BIASI Domenico	Ricercatore	MED/16 REUMATOLOGIA
33	CAPELLI Maria Carla	Ricercatore	MED/09 MEDICINA INTERNA
34	CAPRA Franco	Ricercatore	MED/09 MEDICINA INTERNA
35	CICOIRA Mariantonietta	Ricercatore	MED/11 MALATTIE DELL'APPARATO CARDIO VASCOLARE
36	DALLE CARBONARE Luca Giuseppe	Ricercatore	MED/09 MEDICINA INTERNA
37	DE MARCHI Sergio	Ricercatore	MED/09 MEDICINA INTERNA
38	DEL GIGLIO Micol	Ricercatore	MED/35 MALATTIE CUTANEE E VENEREE
39	DELL'AGNOLA Chiara	Ricercatore	MED/06 ONCOLOGIA MEDICA
40	DELVA Pietro	Ricercatore	MED/09 MEDICINA INTERNA
41	DI FRANCESCO Vincenzo	Ricercatore	MED/09 MEDICINA INTERNA
42	FANTIN Francesco	Ricercatore	MED/09 MEDICINA INTERNA
43	FAVA Cristiano	Ricercatore	MED/09 MEDICINA INTERNA
44	FRACASSI Elena	Ricercatore	MED/16 REUMATOLOGIA
45	FRATTA PASINI Anna Maria	Ricercatore	MED/09 MEDICINA INTERNA
46	FRISO Simonetta	Ricercatore	MED/09 MEDICINA INTERNA
47	GABBRIELLI Armando	Ricercatore	MED/12 GASTROENTEROLOGIA
48	GATTI Davide	Ricercatore	MED/16 REUMATOLOGIA
49	GISONDI Paolo	Ricercatore	MED/35 MALATTIE CUTANEE E VENEREE
50	GUARINI Patrizia	Ricercatore	MED/09 MEDICINA INTERNA
51	KRAMPERA Mauro	Ricercatore	MED/15 MALATTIE DEL SANGUE
52	MARTINELLI Nicola	Ricercatore	MED/09 MEDICINA INTERNA
53	MONTESI Germana Dolores	Ricercatore	MED/09 MEDICINA INTERNA
54	PALUANI Francesca	Ricercatore	MED/09 MEDICINA INTERNA
55	PIZZOLO Francesca	Ricercatore	MED/09 MEDICINA INTERNA
56	RIGO Antonella	Ricercatore	MED/15 MALATTIE DEL SANGUE
57	ROSINA Paolo	Ricercatore	MED/35 MALATTIE CUTANEE E VENEREE
58	ROSSINI Maurizio	Ricercatore	MED/16 REUMATOLOGIA
59	STANZIAL Annamaria	Ricercatore	MED/09 MEDICINA INTERNA
60	TARGHER Giovanni	Ricercatore	MED/13 ENDOCRINOLOGIA
61	TECCHIO Cristina	Ricercatore	MED/15 MALATTIE DEL SANGUE
62	TROMBETTA Maddalena	Ricercatore	MED/13 ENDOCRINOLOGIA
63	VAONA Bruna	Ricercatore	MED/12 GASTROENTEROLOGIA
64	VIAPIANA Ombretta	Ricercatore	MED/16 REUMATOLOGIA
65	ZOCCA Isabella	Ricercatore	MED/09 MEDICINA INTERNA
66	ZOICO Elena	Ricercatore	MED/09 MEDICINA INTERNA
67	ZOPPINI Giacomo	Ricercatore	MED/13 ENDOCRINOLOGIA

PATOLOGIA E DIAGNOSTICA

N.	COGNOME E NOME	RUOLO	SSD
1	BERTON Giorgio	Ordinario	MED/04 PATOLOGIA GENERALE
2	BONETTI Franco	Ordinario	MED/08 ANATOMIA PATOLOGICA
3	CANEPARI Pietro	Ordinario	MED/07 MICROBIOLOGIA E MICROBIOLOGIA CLINICA
4	CASSATELLA Marco Antonio	Ordinario	MED/04 PATOLOGIA GENERALE
5	CHILOSI Marco	Ordinario	MED/08 ANATOMIA PATOLOGICA
6	CONCIA Ercole	Ordinario	MED/17 MALATTIE INFETTIVE
7	FONTANA Roberta	Ordinario	MED/07 MICROBIOLOGIA E MICROBIOLOGIA CLINICA
8	MENESTRINA Fabio	Ordinario	MED/08 ANATOMIA PATOLOGICA
9	POZZI MUCELLI Roberto	Ordinario	MED/36 DIAGNOSTICA PER IMMAGINI E RADIOTERAPIA
10	SCARPA Aldo	Ordinario	MED/08 ANATOMIA PATOLOGICA
11	BAZZONI Flavia	Associato	MED/04 PATOLOGIA GENERALE
12	BELLAVITE Paolo	Associato	MED/04 PATOLOGIA GENERALE
13	CAZZADORI Angelo	Associato	MED/17 MALATTIE INFETTIVE
14	COLOMBATTI Marco	Associato	MED/04 PATOLOGIA GENERALE
15	CORNAGLIA Giuseppe	Associato	MED/07 MICROBIOLOGIA E MICROBIOLOGIA CLINICA
16	DUSI Stefano	Associato	MED/04 PATOLOGIA GENERALE
17	FERDEGHINI Marco	Associato	MED/36 DIAGNOSTICA PER IMMAGINI E RADIOTERAPIA
18	LAUDANNA Carlo	Associato	MED/04 PATOLOGIA GENERALE
19	LLEO' FERNANDEZ Maria Del Mar	Associato	MED/07 MICROBIOLOGIA E MICROBIOLOGIA CLINICA
20	MANFREDI Riccardo	Associato	MED/36 DIAGNOSTICA PER IMMAGINI E RADIOTERAPIA
21	MANSUETO Giancarlo	Associato	MED/36 DIAGNOSTICA PER IMMAGINI E RADIOTERAPIA
22	MARTIGNONI Guido	Associato	MED/08 ANATOMIA PATOLOGICA
23	ZAMBONI Giuseppe	Associato	MED/08 ANATOMIA PATOLOGICA
24	AZZINI Anna Maria	Ricercatore	MED/17 MALATTIE INFETTIVE
25	BOARETTI Marzia	Ricercatore	MED/07 MICROBIOLOGIA E MICROBIOLOGIA CLINICA
26	BRUNELLI Matteo	Ricercatore	MED/08 ANATOMIA PATOLOGICA
27	CARRA Giuseppe	Ricercatore	BIO/10 BIOCHIMICA
28	CONSTANTIN Gabriela	Ricercatore	MED/04 PATOLOGIA GENERALE
29	CONTI Michela	Ricercatore	MED/17 MALATTIE INFETTIVE
30	DELLA BIANCA Vittorina	Ricercatore	MED/04 PATOLOGIA GENERALE
31	D'ONOFRIO Mirko	Ricercatore	MED/36 DIAGNOSTICA PER IMMAGINI E RADIOTERAPIA
32	GEROSA Franca	Ricercatore	MED/04 PATOLOGIA GENERALE
33	MANFRIN Erminia	Ricercatore	MED/08 ANATOMIA PATOLOGICA
34	MAZZARIOL Annarita	Ricercatore	MED/07 MICROBIOLOGIA E MICROBIOLOGIA CLINICA
35	MOMBELLO Aldo	Ricercatore	MED/08 ANATOMIA PATOLOGICA
36	MONSURRO' Vladia	Ricercatore	MED/04 PATOLOGIA GENERALE
37	SARTORIS Silvia	Ricercatore	MED/04 PATOLOGIA GENERALE
38	SCAPINI Patrizia	Ricercatore	MED/04 PATOLOGIA GENERALE
39	SIGNORETTO Caterina	Ricercatore	MED/07 MICROBIOLOGIA E MICROBIOLOGIA CLINICA
40	SORIO Claudio	Ricercatore	MED/04 PATOLOGIA GENERALE
41	ZAMO' Alberto	Ricercatore	MED/08 ANATOMIA PATOLOGICA

SANITA' PUBBLICA E MEDICINA DI COMUNITA'

N.	COGNOME E NOME	RUOLO	SSD	
1	BERTAZZONI MINELLI Elisa	Ordinario	BIO/14	FARMACOLOGIA
2	BURTI Lorenzo	Ordinario	MED/25	PSICHIATRIA
3	DE LEO Domenico	Ordinario	MED/43	MEDICINA LEGALE
4	DE MARCO Roberto	Ordinario	MED/01	STATISTICA MEDICA
5	FUMAGALLI Guido Francesco	Ordinario	BIO/14	FARMACOLOGIA
6	MAJORI Silvia	Ordinario	MED/42	IGIENE GENERALE E APPLICATA
7	PERBELLINI Luigi	Ordinario	MED/44	MEDICINA DEL LAVORO
8	POLI Albino	Ordinario	MED/42	IGIENE GENERALE E APPLICATA
9	ROMANO Gabriele	Ordinario	MED/42	IGIENE GENERALE E APPLICATA
10	RUGGERI Mirella	Ordinario	MED/25	PSICHIATRIA
11	TAGLIARO Franco	Ordinario	MED/43	MEDICINA LEGALE
12	TANSELLA Michele	Ordinario	MED/25	PSICHIATRIA
13	VELO Giampaolo	Ordinario	BIO/14	FARMACOLOGIA
14	ZIMMERMANN Christa	Ordinario	M-PSI/08	PSICOLOGIA CLINICA
15	AMADDEO Francesco	Associato	MED/25	PSICHIATRIA
16	CHIAMULERA Cristiano	Associato	BIO/14	FARMACOLOGIA
17	FRACASSO Maria Enrica	Associato	BIO/14	FARMACOLOGIA
18	LEONE Roberto	Associato	BIO/14	FARMACOLOGIA
19	POLETTINI Aldo Eliano	Associato	MED/43	MEDICINA LEGALE
20	ROMEO Luciano	Associato	MED/44	MEDICINA DEL LAVORO
21	SAIANI Luisa	Associato	MED/45	SCIENZE INFERMIERISTICHE GENERALI, CLINICHE E PEDIATRICHE
22	VERLATO Giuseppe	Associato	MED/01	STATISTICA MEDICA
23	ZANOLIN Maria Elisabetta	Associato	MED/01	STATISTICA MEDICA
24	ACCORDINI Simone	Ricercatore	MED/01	STATISTICA MEDICA
25	BARBUI Corrado	Ricercatore	MED/25	PSICHIATRIA
26	BENONI Giuseppina	Ricercatore	BIO/14	FARMACOLOGIA
27	BORTOLOTTI Federica	Ricercatore	MED/43	MEDICINA LEGALE
28	CAZZOLETTI Lucia	Ricercatore	MED/01	STATISTICA MEDICA
29	CIPRIANI Andrea	Ricercatore	MED/25	PSICHIATRIA
30	CONFORTI Anita	Ricercatore	BIO/14	FARMACOLOGIA
31	CUNICO Laura	Ricercatore	MED/45	SCIENZE INFERMIERISTICHE GENERALI, CLINICHE E PEDIATRICHE
32	CUZZOLIN Laura	Ricercatore	BIO/14	FARMACOLOGIA
33	DEL PICCOLO Lidia	Ricercatore	M-PSI/08	PSICOLOGIA CLINICA
34	FRANCO Luigina	Ricercatore	BIO/14	FARMACOLOGIA
35	GOSS Claudia	Ricercatore	M-PSI/08	PSICOLOGIA CLINICA
36	LOCATELLI Francesca	Ricercatore	MED/01	STATISTICA MEDICA
37	MANTOVANI William	Ricercatore	MED/42	IGIENE GENERALE E APPLICATA
38	MORETTI Ugo	Ricercatore	BIO/14	FARMACOLOGIA
39	PRINCIVALLE Andrea	Ricercatore	MED/44	MEDICINA DEL LAVORO
40	RIMONDINI Michela	Ricercatore	M-PSI/08	PSICOLOGIA CLINICA
41	TARDIVO Stefano	Ricercatore	MED/42	IGIENE GENERALE E APPLICATA
42	TOSATO Sarah	Ricercatore	MED/25	PSICHIATRIA
43	BACCICONI Marina	Assistente	MED/43	MEDICINA LEGALE

SCIENZE DELLA VITA E DELLA RIPRODUZIONE

N.	COGNOME E NOME	RUOLO	SSD	
1	ARMATO Ubaldo	Ordinario	BIO/17	ISTOLOGIA
2	BERTAZZONI Umberto	Ordinario	BIO/11	BIOLOGIA MOLECOLARE
3	BONER Attilio	Ordinario	MED/38	PEDIATRIA GENERALE E SPECIALISTICA
4	DALLA BERNARDINA Bernardo	Ordinario	MED/39	NEUROPSICHIATRIA INFANTILE
5	FRANCHI Massimo	Ordinario	MED/40	GINECOLOGIA E OSTETRICIA
6	GUIDI Giancesare	Ordinario	BIO/12	BIOCHIMICA CLINICA E BIOLOGIA MOLECOLARE E CLINICA
7	MORANDI Carlo	Ordinario	SBIO/13	BIOLOGIA APPLICATA
8	MOTTES Monica	Ordinario	BIO/13	BIOLOGIA APPLICATA
9	PALMIERI Marta	Ordinario	BIO/10	BIOCHIMICA
10	PIGNATTI Pierfranco	Ordinario	MED/03	GENETICA MEDICA
11	SUZUKI Hisanori	Ordinario	BIO/10	BIOCHIMICA
12	VOLTATTORNI Carla	Ordinario	BIO/10	BIOCHIMICA
13	ANTONIAZZI Franco	Associato	MED/38	PEDIATRIA GENERALE E SPECIALISTICA
14	BERTOLDI Mariarita	Associato	BIO/10	BIOCHIMICA
15	BORRUTO Franco	Associato	MED/40	GINECOLOGIA E OSTETRICIA
16	DIANI Franco	Associato	MED/40	GINECOLOGIA E OSTETRICIA
17	MAFFEIS Claudio	Associato	MED/38	PEDIATRIA GENERALE E SPECIALISTICA
18	MENEGAZZI Marta Vittoria	Associato	BIO/10	BIOCHIMICA
19	PADOVANI Ezio Maria	Associato	MED/38	PEDIATRIA GENERALE E SPECIALISTICA
20	PAJNO FERRARA Franco	Associato	MED/39	NEUROPSICHIATRIA INFANTILE
21	PIACENTINI Giorgio	Associato	MED/38	PEDIATRIA GENERALE E SPECIALISTICA
22	PINELLI Leonardo	Associato	MED/38	PEDIATRIA GENERALE E SPECIALISTICA
23	TURCO Alberto	Associato	MED/03	GENETICA MEDICA
24	ZANCONATO Giovanni	Associato	MED/40	GINECOLOGIA E OSTETRICIA
25	BODINI Alessandro	Ricercatore	MED/38	PEDIATRIA GENERALE E SPECIALISTICA
26	BOMBIERI Cristina	Ricercatore	BIO/13	BIOLOGIA APPLICATA
27	CARTOLARI Ignazio	Ricercatore	MED/40	GINECOLOGIA E OSTETRICIA
28	CELLINI Barbara	Ricercatore	BIO/10	BIOCHIMICA
29	CHIARINI Anna Maria	Ricercatore	BIO/17	ISTOLOGIA
30	DAL PRA' Ilaria Pierpaola	Ricercatore	BIO/17	ISTOLOGIA
31	DARRA Francesca	Ricercatore	MED/39	NEUROPSICHIATRIA INFANTILE
32	DONADELLI Massimo	Ricercatore	BIO/10	BIOCHIMICA
33	GAUDINO Rossella	Ricercatore	MED/38	PEDIATRIA GENERALE E SPECIALISTICA
34	GOTTE Giovanni	Ricercatore	BIO/10	BIOCHIMICA
35	LIBOI Elio Maria	Ricercatore	BIO/10	BIOCHIMICA
36	MALERBA Giovanni	Ricercatore	MED/03	GENETICA MEDICA
37	MARCOLONGO Alma	Ricercatore	MED/40	GINECOLOGIA E OSTETRICIA
38	MARIOTTO Sofia Giovanna	Ricercatore	BIO/10	BIOCHIMICA
39	MENAPACE Lia	Ricercatore	BIO/17	ISTOLOGIA
40	RAFFAELLI Ricciarda	Ricercatore	MED/40	GINECOLOGIA E OSTETRICIA
41	ROMANELLI Maria	Ricercatore	BIO/13	BIOLOGIA APPLICATA
42	SALVAGNO Gian Luca	Ricercatore	BIO/12	BIOCHIMICA CLINICA E BIOLOGIA MOLECOLARE E CLINICA
43	SANGALLI Antonella	Ricercatore	BIO/13	BIOLOGIA APPLICATA
44	SILVESTRE Vincenzo	Ricercatore	MED/40	GINECOLOGIA E OSTETRICIA
45	TRABETTI Elisabetta	Ricercatore	BIO/13	BIOLOGIA APPLICATA
46	TURINETTO Anna	Ricercatore	MED/40	GINECOLOGIA E OSTETRICIA
47	ZAFFANELLO Marco	Ricercatore	MED/38	PEDIATRIA GENERALE E SPECIALISTICA
48	ZARDINI Ennio	Ricercatore	MED/40	GINECOLOGIA E OSTETRICIA
49	ZATTI Nicoletta	Ricercatore	MED/40	GINECOLOGIA E OSTETRICIA
50	ZIPETO Donato	Ricercatore	BIO/11	BIOLOGIA MOLECOLARE

SCIENZE ECONOMICHE

N.	COGNOME E NOME	RUOLO	SSD	
1	BERARDI Andrea	Ordinario	SECS-S/06	METODI MATEMATICI DELL'ECONOMIA E DELLE SCIENZE ATTUARIALI E FINANZIARIE
2	BORELLI Giorgio	Ordinario	SECS-P/12	STORIA ECONOMICA
3	BRESSAN Franco	Ordinario	SECS-S/05	STATISTICA SOCIALE
4	CACICI Vincenzo	Ordinario	SECS-S/03	STATISTICA ECONOMICA
5	CIPRIANI Giam Pietro	Ordinario	SECS-P/01	ECONOMIA POLITICA
6	LUBIAN Diego	Ordinario	SECS-P/05	ECONOMETRIA
7	MALLE Silvana	Ordinario	SECS-P/02	POLITICA ECONOMICA
8	OLIVIERI Darionino	Ordinario	SECS-S/01	STATISTICA
9	PEDERZOLI Vittorio	Ordinario	SECS-P/02	POLITICA ECONOMICA
10	PELLEGRINI Letizia	Ordinario	SECS-S/06	METODI MATEMATICI DELL'ECONOMIA E DELLE SCIENZE ATTUARIALI E FINANZIARIE
11	PERALI Carlo Federico	Ordinario	SECS-P/02	POLITICA ECONOMICA
12	ROSSI Francesco	Ordinario	SECS-S/06	METODI MATEMATICI DELL'ECONOMIA E DELLE SCIENZE ATTUARIALI E FINANZIARIE
13	SARTOR Nicola	Ordinario	SECS-P/03	SCIENZA DELLE FINANZE
14	TONDINI Giovanni	Ordinario	SECS-P/02	POLITICA ECONOMICA
15	ZALIN Giovanni	Ordinario	SECS-P/12	STORIA ECONOMICA
16	BARBARANI Francesco	Associato	SECS-P/12	STORIA ECONOMICA
17	DE SINOPOLI Francesco	Associato	SECS-P/01	ECONOMIA POLITICA
18	DOLCI Paolo	Associato	SECS-S/06	METODI MATEMATICI DELL'ECONOMIA E DELLE SCIENZE ATTUARIALI E FINANZIARIE
19	DONGILI Paola	Associato	SECS-P/01	ECONOMIA POLITICA
20	FIORENTINI Riccardo	Associato	SECS-P/01	ECONOMIA POLITICA
21	GAMBA Andrea	Associato	SECS-S/06	METODI MATEMATICI DELL'ECONOMIA E DELLE SCIENZE ATTUARIALI E FINANZIARIE
22	GIACOMELLO Bruno	Associato	SECS-S/06	METODI MATEMATICI DELL'ECONOMIA E DELLE SCIENZE ATTUARIALI E FINANZIARIE
23	GIOVANNETTI Emanuele	Associato	SECS-P/01	ECONOMIA POLITICA
24	GROSSI Luigi	Associato	SECS-S/03	STATISTICA ECONOMICA
25	MINOZZO Marco	Associato	SECS-S/01	STATISTICA
26	MONTRESOR Elisa	Associato	AGR/01	ECONOMIA ED ESTIMO RURALE
27	PEGRARI Maurizio	Associato	SECS-P/12	STORIA ECONOMICA
28	PERETTI Alberto	Associato	SECS-S/06	METODI MATEMATICI DELL'ECONOMIA E DELLE SCIENZE ATTUARIALI E FINANZIARIE
29	SAVI Paola	Associato	M-GGR/02	GEOGRAFIA ECONOMICO POLITICA
30	SPILLER Cristina	Associato	SECS-P/01	ECONOMIA POLITICA
31	VIVENZA Gloria	Associato	SECS-P/04	STORIA DEL PENSIERO ECONOMICO
32	ZOLI Claudio	Associato	SECS-P/03	SCIENZA DELLE FINANZE
33	BUCCIOL Alessandro	Ricercatore	SECS-P/05	ECONOMETRIA
34	CENTANNI Silvia	Ricercatore	SECS-S/06	METODI MATEMATICI DELL'ECONOMIA E DELLE SCIENZE ATTUARIALI E FINANZIARIE
35	CICOGNA Veronica	Ricercatore	SECS-S/01	STATISTICA
36	DEMO Edoardo	Ricercatore	SECS-P/12	STORIA ECONOMICA
37	FERRARI Maria Luisa	Ricercatore	M-STO/04	STORIA CONTEMPORANEA
38	GUOLO Annamaria	Ricercatore	SECS-S/01	STATISTICA
39	MAGAZZINI Laura	Ricercatore	SECS-P/05	ECONOMETRIA
40	MARIUTTI Gianpaolo	Ricercatore	SECS-P/01	ECONOMIA POLITICA
41	MENON Martina	Ricercatore	SECS-P/01	ECONOMIA POLITICA
42	NOTO Sergio	Ricercatore	SECS-P/12	STORIA ECONOMICA
43	PECCI Francesco	Ricercatore	AGR/01	ECONOMIA ED ESTIMO RURALE
44	PELUSO Eugenio	Ricercatore	SECS-P/02	POLITICA ECONOMICA
45	PERTILE Paolo	Ricercatore	SECS-P/03	SCIENZA DELLE FINANZE
46	POLIN Veronica	Ricercatore	SECS-P/03	SCIENZA DELLE FINANZE
47	ROVEDA Alberto	Ricercatore	SECS-P/06	ECONOMIA APPLICATA
48	ROVENTINI Andrea	Ricercatore	SECS-P/01	ECONOMIA POLITICA
49	SIRONI Michela	Ricercatore	SECS-P/02	POLITICA ECONOMICA
50	SOMMACAL Alessandro	Ricercatore	SECS-P/03	SCIENZA DELLE FINANZE
51	TEBALDI Claudio	Ricercatore	SECS-S/06	METODI MATEMATICI DELL'ECONOMIA E DELLE SCIENZE ATTUARIALI E FINANZIARIE
52	VAONA Andrea	Ricercatore	SECS-P/01	ECONOMIA POLITICA
53	ZAGO Angelo	Ricercatore	SECS-P/01	ECONOMIA POLITICA
54	ZARRI Luca	Ricercatore	SECS-P/02	POLITICA ECONOMICA

SCIENZE GIURIDICHE

N.	COGNOME E NOME	RUOLO	SSD	
1	ALBERTI Giovanni Battista	Ordinario	SECS-P/07	ECONOMIA AZIENDALE
2	BARUFFI Maria Caterina	Ordinario	IUS 13	DIRITTO INTERNAZIONALE
3	CAVALERI Paolo	Ordinario	IUS 09	ISTITUZIONI DI DIRITTO PUBBLICO
4	CORLETTO Daniele	Ordinario	IUS 10	DIRITTO AMMINISTRATIVO
5	DURET Paolo	Ordinario	IUS 10	DIRITTO AMMINISTRATIVO
6	FERRARI Franco	Ordinario	IUS 13	DIRITTO INTERNAZIONALE
7	GENOVESE Anna	Ordinario	IUS 04	DIRITTO COMMERCIALE
8	GOTTARDI Donata Maria Assunta	Ordinario	IUS 07	DIRITTO DEL LAVORO
9	MESSINA Sebastiano Maurizio	Ordinario	IUS 12	DIRITTO TRIBUTARIO
10	NATUCCI Alessandro	Ordinario	IUS 01	DIRITTO PRIVATO
11	PATRONO Paolo	Ordinario	IUS 17	DIRITTO PENALE
12	PEDRAZZA GORLERO Maurizio	Ordinario	IUS 08	DIRITTO COSTITUZIONALE
13	PICOTTI Lorenzo	Ordinario	IUS 17	DIRITTO PENALE
14	PRESUTTI Adonella	Ordinario	IUS 16	DIRITTO PROCESSUALE PENALE
15	RIGUZZI Maurizio	Ordinario	IUS 06	DIRITTO DELLA NAVIGAZIONE
16	RUSCELLO Francesco	Ordinario	IUS 01	DIRITTO PRIVATO
17	SALA Giovanni Antonio	Ordinario	IUS 10	DIRITTO AMMINISTRATIVO
18	TANTINI Giovanni	Ordinario	IUS 04	DIRITTO COMMERCIALE
19	TOMMASEO Ferruccio	Ordinario	IUS 15	DIRITTO PROCESSUALE CIVILE
20	TROIANO Stefano	Ordinario	IUS 01	DIRITTO PRIVATO
21	ZACCARIA Alessio	Ordinario	IUS 01	DIRITTO PRIVATO
22	ZANUSO Francesca	Ordinario	IUS 20	FILOSOFIA DEL DIRITTO
23	CALAFA' Laura	Associato	IUS 07	DIRITTO DEL LAVORO
24	CIAMPI Annalisa	Associato	IUS 13	DIRITTO INTERNAZIONALE
25	COMOTTI Giuseppe	Associato	IUS 11	DIRITTO ECCLESIASTICO E CANONICO
26	DALLA MASSARA Tommaso	Associato	IUS 18	DIRITTO ROMANO E DIRITTI DELL'ANTICHITÀ
27	DALLE VEDOVE Giampaolo	Associato	IUS 04	DIRITTO COMMERCIALE
28	DE MARI Michele	Associato	IUS 04	DIRITTO COMMERCIALE
29	FERRI Giampietro	Associato	IUS 08	DIRITTO COSTITUZIONALE
30	FUSELLI Stefano	Associato	IUS 20	FILOSOFIA DEL DIRITTO
31	GUIGLIA Giovanni	Associato	IUS 09	ISTITUZIONI DI DIRITTO PUBBLICO
32	LAMBRINI Paola	Associato	IUS 08	DIRITTO COSTITUZIONALE
33	MERUZZI Giovanni	Associato	IUS 04	DIRITTO COMMERCIALE
34	ORTINO Matteo	Associato	IUS 05	DIRITTO DELL'ECONOMIA
35	PALERMO Francesco	Associato	IUS 21	DIRITTO PUBBLICO COMPARATO
36	PILATI Andrea	Associato	IUS 07	DIRITTO DEL LAVORO
37	RENON Paolo	Associato	IUS 16	DIRITTO PROCESSUALE PENALE
38	ROSSI Giovanni	Associato	IUS 19	STORIA DEL DIRITTO MEDIEVALE E MODERNO
39	BERCELLI Jacopo	Ricercatore	IUS 10	DIRITTO AMMINISTRATIVO
40	BUTTURINI Paolo	Ricercatore	IUS 04	DIRITTO COMMERCIALE
41	CARLOTTO Ilaria	Ricercatore	IUS 09	ISTITUZIONI DI DIRITTO PUBBLICO
42	CORDIANO Alessandra	Ricercatore	IUS 01	DIRITTO PRIVATO
43	CRIVELLI Elisabetta	Ricercatore	IUS 08	DIRITTO COSTITUZIONALE
44	FACCIOLI Mirko	Ricercatore	IUS 01	DIRITTO PRIVATO
45	GRENDENE Igino	Ricercatore	IUS 03	DIRITTO AGRARIO
46	LIGUGNANA Giovanna	Ricercatore	IUS 10	DIRITTO AMMINISTRATIVO
47	MILANO Enrico	Ricercatore	IUS 13	DIRITTO INTERNAZIONALE
48	NADALET Sylvain Giovanni	Ricercatore	IUS 07	DIRITTO DEL LAVORO
49	OMODEI SALE' Riccardo	Ricercatore	IUS 01	DIRITTO PRIVATO
50	ONNIBONI Claudia	Ricercatore	IUS 15	DIRITTO PROCESSUALE CIVILE
51	PANZERI Lino	Ricercatore	IUS 09	ISTITUZIONI DI DIRITTO PUBBLICO
52	PASQUARIELLO Federica	Ricercatore	IUS 04	DIRITTO COMMERCIALE
53	PEDRAZZA GORLERO Cecilia	Ricercatore	IUS 19	STORIA DEL DIRITTO MEDIEVALE E MODERNO
54	PELLOSO Carlo	Ricercatore	IUS 18	DIRITTO ROMANO E DIRITTI DELL'ANTICHITÀ
55	SALOMONI Alessandra	Ricercatore	IUS 01	DIRITTO PRIVATO
56	STRANO Silvana	Ricercatore	IUS 17	DIRITTO PENALE
57	TESCARO Mauro	Ricercatore	IUS 01	DIRITTO PRIVATO
58	TINCANI Chiara	Ricercatore	IUS 06	DIRITTO DELLA NAVIGAZIONE
59	TRABUCCHI Giuseppe	Ricercatore	IUS 04	DIRITTO COMMERCIALE
60	VELO DALBRENTA Daniele	Ricercatore	IUS 20	FILOSOFIA DEL DIRITTO
61	ZINI Francesco	Ricercatore	IUS 20	FILOSOFIA DEL DIRITTO

SCIENZE NEUROLOGICHE, NEUROPSICOLOGICHE, MORFOLOGICHE E MOTORIE

N.	COGNOME E NOME	RUOLO	SSD	
1	BENTIVOGLIO FALES Marina	Ordinario	BIO/17	ISTOLOGIA
2	BERLUCCHI Giovanni	Ordinario	BIO/09	FISIOLOGIA
3	CAPELLI Carlo	Ordinario	BIO/09	FISIOLOGIA
4	CEVESE Antonio	Ordinario	M-EDF/01	METODI E DIDATTICHE DELLE ATTIVITA' MOTORIE
5	CHELAZZI Leonardo	Ordinario	BIO/09	FISIOLOGIA
6	FIASCHI Antonio	Ordinario	MED/26	NEUROLOGIA
7	GEROSA Massimo	Ordinario	MED/27	NEUROCHIRURGIA
8	MARCHINI Giorgio	Ordinario	MED/30	MALATTIE APPARATO VISIVO
9	MARZI Carlo Alberto	Ordinario	M-PSI/01	PSICOLOGIA GENERALE
10	MONACO Salvatore	Ordinario	MED/26	NEUROLOGIA
11	SBARBATI Andrea	Ordinario	BIO/16	ANATOMIA UMANA
12	SCHENA Federico	Ordinario	M-EDF/02	METODI E DIDATTICHE DELLE ATTIVITA' SPORTIVE
13	TASSINARI Giancarlo	Ordinario	BIO/09	FISIOLOGIA
14	ZANCANARO Carlo	Ordinario	BIO/16	ANATOMIA UMANA
15	BASSETTO Maria Antonietta	Associato	MED/02	STORIA DELLA MEDICINA
16	BONETTI Bruno	Associato	MED/26	NEUROLOGIA
17	BUFFELLI Mario Rosario	Associato	BIO/09	FISIOLOGIA
18	FABRIZI Gian Maria	Associato	MED/26	NEUROLOGIA
19	GIRELLI Massimo	Associato	M-PSI/01	PSICOLOGIA GENERALE
20	PASINO Efrem	Associato	BIO/09	FISIOLOGIA
21	SIMONATI Alessandro	Associato	MED/26	NEUROLOGIA
22	SMANIA Nicola	Associato	MED/34	MEDICINA FISICA E RIABILITATIVA
23	TINAZZI Michele	Associato	MED/26	NEUROLOGIA
24	ZAMPARO Paola	Associato	M-EDF/01	METODI E DIDATTICHE DELLE ATTIVITA' MOTORIE
25	ARDIGO' Luca Paolo	Ricercatore	M-EDF/02	METODI E DIDATTICHE DELLE ATTIVITA' SPORTIVE
26	BERTINATO Luciano	Ricercatore	M-EDF/02	METODI E DIDATTICHE DELLE ATTIVITA' SPORTIVE
27	BERTINI Giuseppe	Ricercatore	BIO/17	ISTOLOGIA
28	BONGIOVANNI Luigi Giuseppe	Ricercatore	MED/26	NEUROLOGIA
29	BUSETTO Giuseppe	Ricercatore	BIO/09	FISIOLOGIA
30	CALDERAN Laura	Ricercatore	BIO/16	ANATOMIA UMANA
31	CASATI Stefano	Ricercatore	MED/30	MALATTIE APPARATO VISIVO
32	CESARI Paola	Ricercatore	M-EDF/01	METODI E DIDATTICHE DELLE ATTIVITA' MOTORIE
33	FABENE Paolo	Ricercatore	BIO/16	ANATOMIA UMANA
34	FENZI Flavio	Ricercatore	MED/26	NEUROLOGIA
35	GALIE' Mirco	Ricercatore	BIO/16	ANATOMIA UMANA
36	GALMONTE Alessandra	Ricercatore	M-PSI/01	PSICOLOGIA GENERALE
37	LANZA Massimo	Ricercatore	M-EDF/02	METODI E DIDATTICHE DELLE ATTIVITA' SPORTIVE
38	MALATESTA Manuela	Ricercatore	BIO/16	ANATOMIA UMANA
39	MANGANOTTI Paolo	Ricercatore	MED/26	NEUROLOGIA
40	MARIOTTI Raffaella	Ricercatore	BIO/17	ISTOLOGIA
41	MAZZUCCO Sara	Ricercatore	MED/26	NEUROLOGIA
42	MILANESE Chiara	Ricercatore	M-EDF/02	METODI E DIDATTICHE DELLE ATTIVITA' SPORTIVE
43	MORBIO Roberta	Ricercatore	MED/30	MALATTIE APPARATO VISIVO
44	PEDROTTI Emilio	Ricercatore	MED/30	MALATTIE APPARATO VISIVO
45	POGLIAGHI Silvia	Ricercatore	BIO/09	FISIOLOGIA
46	POLTRONIERI Roberto	Ricercatore	BIO/09	FISIOLOGIA
47	SALA Francesco	Ricercatore	MED/27	NEUROCHIRURGIA
48	SALVIATI Alessandro	Ricercatore	MED/26	NEUROLOGIA
49	SAVAZZI Silvia	Ricercatore	M-PSI/01	PSICOLOGIA GENERALE
50	TALACCHI Andrea	Ricercatore	MED/27	NEUROCHIRURGIA
51	TAMBURIN Stefano	Ricercatore	MED/26	NEUROLOGIA
52	TOMELLERI Giuliano	Ricercatore	MED/26	NEUROLOGIA
53	VATTEMI Gaetano Nicola	Ricercatore	MED/26	NEUROLOGIA
54	ZANUSSO Gianluigi	Ricercatore	MED/26	NEUROLOGIA

UNIVERSITÀ DEGLI STUDI DI VERONA
Area degli Affari Generali

BC/ep

Prot. 17133
Tit. VI/3

Verona, 29/03/2010

UNIVERSITA' DEGLI STUDI DI VERONA *Dipartimento di Scienze Biomediche e Chirurgiche*		
Titolo II Classe 10 Fascicolo		
PROT. N. 35 DEL 02/04/10		
UOR DSBC	CC	RPA

Chiar.mo Prof. Antonio Lupo
Dipartimento di Medicina

e, p.c. Alla Segreteria del Dipartimento di Medicina

LORO SEDI

OGGETTO: Nomina a Direttore del Dipartimento di Medicina.

Si ha il piacere di comunicare che la S.V. Ill.ma è stata nominata, con decreto rettorale che si allega, Direttore del Dipartimento di Medicina per il rimanente periodo del triennio accademico 2009/2010 - 2010/2011 - 2011/2012.

E' gradita l'occasione per formulare i migliori voti augurali per la preziosa collaborazione che certamente svolgerà a favore del nostro Ateneo.

Cordiali saluti.

IL RESPONSABILE
(Dott.ssa Barbara Caracciolo)
Barbara Caracciolo

Si allega: Decreto Rettorale n. 912 del 29 marzo 2010

U.O. Affari Generali
Tel. 045.802.8282 – fax 045.802.8003 - Via dell'Artigliere n. 8 – 37129 Verona

UNIVERSITÀ DEGLI STUDI DI VERONA
Area Affari Generali e Legali

BC/ep

Decreto n. 912
del 29/03/2010
Prot. n. 16911

IL RETTORE

VISTO lo Statuto emanato con Decreto Rettorale 7 ottobre 1994 n. 6435, modificato con Decreto Rettorale 23 giugno 2000 n.11448, con Decreto Rettorale 8 gennaio 2002 n. 2, con Decreto Rettorale 25 agosto 2005 n. 1624 e, da ultimo, con Decreto Rettorale 14 gennaio 2010 n. 127 ed, in particolare, l'art. 34 in materia di Direttori di Dipartimento;

VISTO il Regolamento Generale d'Ateneo, Parte I, emanato con Decreto Rettorale 25 settembre 1997 n. 8999, modificato con Decreto Rettorale 14 gennaio 2010 n. 127 ed, in particolare, l'art. 42 relativo all'elezione del Direttore di Dipartimento;

VISTO il Regolamento Quadro di Funzionamento dei Dipartimenti emanato con Decreto Rettorale 14 gennaio 2010 n. 131 ed, in particolare, il Titolo III, Capo I relativo all'elezione del Direttore di Dipartimento;

VISTO il Decreto Rettorale 17 febbraio 2010 n. 490 di istituzione del Dipartimento di Medicina;

VISTO il Decreto Rettorale 1° marzo 2010 n. 647 di attivazione del Dipartimento di Medicina;

VISTI gli atti della Commissione Elettorale, costituita i sensi dell'art. 42, comma 5 del Regolamento Generale di Ateneo e dell'art. 22, comma 5 del Regolamento Quadro di Funzionamento dei Dipartimenti, relativi alla votazione effettuata in data 25 marzo 2010 per l'elezione del Direttore del Dipartimento di Medicina per il rimanente periodo del triennio accademico 2009/2010, 2010/2011, 2011/2012;

TENUTO CONTO che nella seduta del Consiglio Straordinario di Dipartimento del 25 marzo 2010 è risultato eletto il Prof. Antonio Lupo, Ordinario per il settore scientifico disciplinare MED/14 *"Nefrologia"*;

VISTA la dichiarazione di accettazione della carica e l'opzione di regime a tempo pieno rilasciate dal Prof. Antonio Lupo ai sensi dell'art. 34, comma 3, dello Statuto;

DECRETA

il **Prof. Antonio Lupo**, Ordinario per il settore scientifico disciplinare MED/14 *"Nefrologia"*, è nominato Direttore del Dipartimento di Medicina per il rimanente periodo del triennio accademico 2009/2010, 2010/2011, 2011/2012.

IL RETTORE
(Prof. Alessandro Mazzucco)

Attachment 4: Official documents justifying the modification of partner #5 POLICLINICO

OSPEDALE MAGGIORE POLICLINICO,
MANGIAGALLI E REGINA ELENA
FONDAZIONE I.R.C.C.S. DI DIRITTO PUBBLICO

ESTRATTO DAL REGISTRO ORIGINALE DELLE DETERMINAZIONI DEL DIRETTORE GENERALE

DETERMINAZIONE N. 3011 DEL 17 DIC. 2009 Atti n. 1290/2009 . All. 33

MODIFICA ART. 1 STATUTO RELATIVA ALLA NUOVA DENOMINAZIONE ENTE – DECORRENZA.

IL DIRETTORE GENERALE

RICHIAMATA la deliberazione n. 14 del 6 novembre 2009 con la quale il Consiglio di Amministrazione approvava la modifica della denominazione della Fondazione IRCCS "Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena", in Fondazione IRCCS "Cà Granda – Ospedale Maggiore Policlinico", con ciò modificando l'art. 1 dello Statuto;

RICORDATO che detta modifica veniva sottoposta alla approvazione della Giunta Regionale;

VISTA la deliberazione n. VIII/010755 dell'11.12.2009 con la quale la Giunta Regionale Lombardia dispone:
"di approvare la modifica della denominazione della Fondazione IRCCS "Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena" oramai "Fondazione IRCCS Cà Granda – Ospedale Maggiore Policlinico";

RITENUTO di prendere atto di quanto come sopra formalizzato dalla Giunta Regionale con il citato provvedimento n. 10755/2009, assumendo – per esigenze tecniche legate ad aspetti contabili, fiscali, assicurativi ecc. – l' 1.1.2010 quale data di decorrenza della nuova denominazione;

PREVIO parere favorevole del Direttore Sanitario e del Direttore Amministrativo;

DETERMINA

1. di prendere atto di quanto deliberato dalla Giunta Regionale con provvedimento n. 10755 del 11.12.2009 circa l'approvazione della diversa denominazione della Fondazione in Fondazione IRCCS "Cà Granda – Ospedale Maggiore Policlinico";
2. di stabilire – per la motivazione indicata in premessa – all' 1.1.2010 la data di decorrenza della nuova denominazione;
3. di avviare, conseguentemente, le notifiche di detta modifica agli enti pubblici e privati e a terzi interessati.

IL DIRETTORE GENERALE
(Dott. Giuseppe Di Benedetto)

IL DIRETTORE SANITARIO
(Dott. Marco Triulzi)

IL DIRETTORE AMMINISTRATIVO
(Dott. Roberto Midolo)

Procedimento presso: Direzione Amministrativa
Responsabile della procedura: Dott. Roberto Midolo
Pratica trattata da: Augusta Medici

17 DIC. 2009 3011

OSPEDALE MAGGIORE POLICLINICO, MANGIAGALLI E REGINA ELENA
FONDAZIONE I.R.C.C.S. DI NATURA PUBBLICA

P	A	CONSIGLIO DI AMMINISTRAZIONE	
X		PRES.	GINANNI GIANCARLO
X		CONS.	SANDERA ADRIANO
X		CONS.	CAMPAGNA FRANCESCO
X		CONS.	COLOMBO SVEVO MARIA PAOLA
X		CONS.	DECLEVA ENRICO
X		CONS.	PEROSSI GABRIELE
X		CONS.	RICCIARDI GIUSEPPE
X		CONS.	ROTH LUIGI
X		DIR. GEN.	DI BENEDETTO GIUSEPPE
X		DIR. SCIENT.	BONINO FERRUCCIO

ESTRATTO DAL REGISTRO ORIGINALE DEI VERBALI DEL CONSIGLIO DI AMMINISTRAZIONE

DELIBERAZIONE N. 14 **DEL** 6 NOV. 2009 **Atti n. 1290/2009 all. 33**

MODIFICA DEL NOME DELLA FONDAZIONE IN FONDAZIONE IRCCS "CA' GRANDA – OSPEDALE MAGGIORE POLICLINICO"

IL CONSIGLIO DI AMMINISTRAZIONE

Premesso che lo Statuto della Fondazione, così come approvato con Decreto del Ministero della Salute del 29 dicembre 2004, all'articolo 1 riporta la denominazione di **Fondazione IRCCS "Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena"**;

Considerato che detta denominazione voleva, con la sua lunga composizione, accompagnare l'apporto delle singole strutture a quell'importante progetto di integrazione in una nuova grande istituzione, che si può ormai definire compiuto anche dal punto di vista organizzativo;

Considerato, altresì, che il rafforzamento dell'identità e la sottolineatura delle radici storiche della Fondazione costituiscono acclarati elementi importanti di coesione interna e di riconoscibilità esterna e, quindi, strumenti primari di comunicazione di valori condivisi;

Ritenuta l'opportunità di denominare la Fondazione con un'accezione che faccia più direttamente appello al sentire comune e alle radici storiche del luogo che la ospita, richiamando il termine "Ca' Granda" (della SS. Annunziata), ovvero - come ricorda Giovanni Testori – "*casa grande*" (magna domus hospitalis), appellativo popolare che, fin dai tempi di erezione dell'edificio progettato dal Filarete per la destinazione sanitaria, identifica la "*casa di ognuno, di chi lungo il giro dei tempi la casa non riuscì mai ad avere, casa che dà ospitalità a tutti, perciò casa grande*"(G. Testori);

Individuata, quindi, la migliore denominazione in: ***Fondazione IRCCS " Ca' Granda – Ospedale Maggiore Policlinico"***;

Ritenuto, alla luce di quanto sopra, di procedere alla conseguente modifica statutaria, indicando la suddetta denominazione all'articolo 1 dello Statuto della Fondazione, e di trasmettere al Presidente della Regione Lombardia il nuovo testo dell'**art. 1: Denominazione e sede**, così modificato:

"*La Fondazione denominata "Fondazione IRCCS "Ca' Granda – Ospedale Maggiore Policlinico"", con sede in Milano, Via Francesco Sforza n. 28, è disciplinata dalle disposizioni di cui al presente Statuto nonché dall'articolo 42 della Legge 16 gennaio 2003 n. 3 e dal Decreto Legislativo 16 ottobre 2003 n. 288.*

La Fondazione non ha scopo di lucro e ha durata illimitata."

Ritenuto, infine, di dover richiedere l'approvazione da parte della Regione Lombardia;

Visto l'art. 14 del vigente Statuto;

previa votazione resa ai sensi di legge, da cui risultano n. 8 voti favorevoli su n. 8 votanti,

OSPEDALE MAGGIORE POLICLINICO, MANGIAGALLI E REGINA ELENA
FONDAZIONE I.R.C.C.S. DI NATURA PUBBLICA

P	A	CONSIGLIO DI AMMINISTRAZIONE	
X		PRES.	CESANA GIANCARLO
X		CONS.	BANDERA ADRIANO
X		CONS.	CAMPAGNA FRANCESCO
X		CONS.	COLOMBO SVEVO MARIA PAOLA
X		CONS.	DECLEVA ENRICO
X		CONS.	PEROSSI GABRIELE
X		CONS.	RICCIARDI GIUSEPPE
X		CONS.	ROTH LUIGI
X		DIR. GEN.	DI BENEDETTO GIUSEPPE
X		DIR. SCIEN.	BONINO FERUCCIO

ESTRATTO DAL REGISTRO ORIGINALE DEI VERBALI DEL CONSIGLIO DI AMMINISTRAZIONE

DELIBERAZIONE N. 14 **DEL** 6 NOV. 2009 **Atti n. 1290/2009 all. 33**

DELIBERA

1. di approvare, per le motivazioni di cui in premessa, la modifica dell'articolo 1 dello Statuto della Fondazione, indicando la denominazione dell'Ente nel seguente modo: **Fondazione IRCCS "Ca' Granda – Ospedale Maggiore Policlinico";**
2. di dare mandato al Presidente della Fondazione di inoltrare al Presidente della Regione Lombardia la suddetta modifica statutaria per la relativa approvazione;
3. di dare atto che il presente provvedimento non comporta impegni di spesa.

IL PRESIDENTE
Prof. Giancarlo Cesana

6 NOV. 2009 14

FONDAZIONE IRCCS CA' GRANDA
OSPEDALE MAGGIORE POLICLINICO

P	A	CONSIGLIO DI AMMINISTRAZIONE	
X		PRES.	CESANA GIANCARLO
X		CONS.	BANDERA ADRIANO
X		CONS.	CAMPAGNA FRANCESCO
X		CONS.	CECCHIN STEFANO
X		CONS.	DICLUVA ENRICO
X		CONS.	FERRONI GABRIELE
X		CONS.	PESSINA PAOLA
X	X	CONS.	RICCIARDI GIUSEPPE
X		DIR. GEN.	DI BENEDETTO GIUSEPPE
X		DIR. SCIEN.	MANNUCCI PIER MANNUCCIO (F.F.)

ESTRATTO DAL REGISTRO ORIGINALE DEI VERBALI DEL CONSIGLIO DI AMMINISTRAZIONE

DELIBERAZIONE N. 34 del 30 LUG. 2010 Atti n. 1221/2010 all. 2

NOMINA DEL DIRETTORE GENERALE DELLA FONDAZIONE IRCCS CA' GRANDA – OSPEDALE MAGGIORE POLICLINICO.

IL CONSIGLIO DI AMMINISTRAZIONE

PREMESSO che lo Statuto della Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico prevede, all'art. 16, che il Direttore Generale della Fondazione medesima è nominato dal Consiglio di Amministrazione su indicazione del Presidente della regione Lombardia;

VISTO il D.P.G.R. del 17 luglio 2009 n. 7417 con il quale veniva indicato quale Direttore Generale della Fondazione il Dott. Giuseppe Di Benedetto, successivamente nominato dal Consiglio di Amministrazione con deliberazione n. 3 del 29 luglio 2009;

DATO ATTO che:

- Il Dott. Di Benedetto, con lettera del 31 maggio 2010, ha comunicato al Presidente le proprie dimissioni anticipate dall'incarico;
- Il Consiglio di Amministrazione ne prende atto con deliberazione n. 32 del 18 giugno 2010, inoltrata al Presidente della Giunta Regionale, al fine di ottenere nuova indicazione per la nomina del Direttore Generale entro il decorrere del termine contrattuale di preavviso di almeno sessanta giorni;

VISTO il decreto n. 7621 del 30 luglio 2010 con il quale il Presidente della Regione Lombardia indica, ai sensi dell'art. 16 dello Statuto, quale Direttore Generale della Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico il Dott. Luigi Macchi, iscritto nell'elenco degli idonei alla nomina di Direttore Generale delle ASL e delle Aziende Ospedaliere;

PREVIA votazione resa ai sensi di legge da cui risultano n. 7 voti favorevoli su n. 7 votanti;

DELIBERA

1. di prendere atto che, con decreto n. 7621 del 30 luglio 2010, il Presidente della Giunta Regionale ha indicato il Dott. Luigi Macchi quale Direttore Generale della Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico;
2. di nominare, nel quadro di quanto riportato in premessa, il Dott. Luigi MACCHI nella funzione di Direttore Generale della Fondazione, con decorrenza 1 agosto 2010;
3. di demandare al Presidente la stipula del contratto di lavoro con il Direttore Generale secondo il testo in atti n. 1221/2010 all. 3.

IL PRESIDENTE
Giancarlo Cesana

REGISTRATA NEL VERBALE DELLE DELIBERAZIONI
IN DATA 30 LUG. 2010 AL N. 34

Attachment 5: Official documents justifying the legal situation of partner #11 UAM

CONVENIO ENTRE EL INSTITUTO MADRILEÑO DE LA SALUD Y LA FUNDACIÓN PARA LA INVESTIGACIÓN BIOMÉDICA DEL HOSPITAL UNIVERSITARIO PUERTA DE HIERRO, SOBRE LA ARTICULACIÓN DE RELACIONES ENTRE LAS FUNDACIONES PARA LA INVESTIGACION BIOMÉDICA Y LOS CENTROS HOSPITALARIOS.

En Madrid, a 7 de julio de 2004

REUNIDOS

De una parte el Ilmo. Sr. D. Jorge Tapia Sáez, Director General del Instituto Madrileño de la Salud, en uso de las atribuciones conferidas por el artículo 9.2 a) del Decreto 145/2002, de 1 de agosto, por el que se establece el Régimen Jurídico y de Funcionamiento del Instituto Madrileño de la Salud, y en uso de la facultad establecida en el artículo 4.3. b) de la Ley 8/1999, de 9 de abril, de adecuación de la normativa de la Comunidad de Madrid a la Ley Estatal 4/1999, de 13 de enero, en la redacción dada por la Ley 1/2001, de 29 de marzo.

Y, de otra, Don Javier Carro González, en calidad de Presidente del Patronato de la Fundación para la Investigación Biomédica del Hospital Universitario Puerta de Hierro, en representación de dicha Fundación, de acuerdo con lo previsto en el artículo 20 de los Estatutos aprobados por Decreto 188/2003, de 24 de julio, por el que se autoriza la constitución de la Fundación para la Investigación Biomédica del Hospital Universitario Puerta de Hierro.

EXPONEN

I. Que, de conformidad con lo dispuesto en el Decreto 48/2003, de 3 de abril, que modifica el Decreto 197/2002, de 26 de diciembre, por el que se establece la estructura orgánica del Instituto Madrileño de la Salud, el Hospital Universitario Puerta de Hierro está adscrito a dicho organismo.

II. Que la Fundación es una entidad sin ánimo de lucro, constituida de acuerdo con lo previsto en el Decreto 188/2003, de 24 de julio, por el que se autoriza la constitución de la Fundación para la Investigación Biomédica del Hospital Universitario Puerta de Hierro, sujeta a lo dispuesto en la Ley 1/1998, de 2 de marzo, de Fundaciones de la Comunidad de Madrid, a la Ley 50/2002, de 26 de diciembre, de Fundaciones y la Ley 49/ 2002 de 23 de diciembre, de Régimen Fiscal de las Entidades sin Fines Lucrativos y de los Incentivos Fiscales al Mecenazgo, así como a los Decretos de desarrollo de las citadas leyes.

III. El artículo 30.2 de los Estatutos, por el que se autoriza la constitución de la Fundación, prevé que "*El Patronato de la Fundación acordará a través de Convenio, las relaciones de cooperación y de coordinación de actividades, así como las relaciones económicas entre la Fundación y el Centro Hospitalario, sin perjuicio de la autonomía de gestión que a la Fundación corresponde y del criterio de caja única que ésta observa*".

IV. Que los fines fundacionales de la Fundación son servir al interés general, dotando al Hospital de un instrumento que sirva de cauce para el impulso y desarrollo de la investigación científico – técnica en el campo de la Biomedicina y las Ciencias de la Salud.

V. Que la investigación biomédica, junto con la asistencia y la docencia, es una función básica de los hospitales universitarios, que incide directamente en la calidad asistencial y cuyos resultados son un producto de la actividad hospitalaria.

VI. Que en el proceso de constitución de la Fundación, el Hospital Universitario Puerta de Hierro ha tenido un papel fundamental, ya que se concibe la Fundación como el instrumento del que se dota la estructura hospitalaria para promocionar y gestionar las actividades de investigación que se llevan a cabo en el Hospital, a través de sus profesionales y cuyo resultado será un producto de la actividad hospitalaria.

VII. Que la Fundación entiende que sus objetivos quedan plenamente cumplidos al dotar al Hospital de un nuevo instrumento de gestión y apoyo a la investigación, que viene a complementar las actuaciones que, hasta el momento, se han llevado a cabo en este ámbito.

VIII. Que para la consecución de las finalidades de ambas instituciones es conveniente establecer el marco de colaboración que ha de regir sus relaciones y por ello acuerdan suscribir el presente Convenio con arreglo a las siguientes

CLÁUSULAS

Primera.- Objeto del Convenio

En desarrollo del artículo 30.2 de los Estatutos, por el que se autoriza la constitución de la Fundación, el objeto de este Convenio es establecer el marco de colaboración entre el Hospital y la Fundación, regulando las relaciones entre ambos, en el desarrollo de las actividades de interés mutuo que contribuyan al logro de las finalidades y objetivos de las dos instituciones.

Segunda.- Definición de las actividades

Las actividades a desarrollar en el marco del presente convenio son entre otras:

2.1 - Promocionar, impulsar y coordinar la investigación Biomédica, entendida en el sentido más amplio del término, tanto la investigación básica como aplicada, clínica, epidemiológica y gestión de servicios sanitarios.

2.2- Impulsar la divulgación de los conocimientos científicos entre los profesionales y pacientes del Hospital, y proyectar al conjunto del sector sanitario, y a la sociedad en general, los avances en el conocimiento científico y sus aplicaciones practicas para la mejora de la calidad asistencial y de la salud de los ciudadanos.

2.3 - Fomentar la formación de personal investigador y de apoyo a la investigación, en colaboración con la Universidad Autónoma de Madrid y las Instituciones públicas y privadas que dirigen sus actividades en este campo, en especial la Agencia Pedro Laín Entralgo.

2.4 - Desarrollar un modelo de gestión, del proceso investigador en el Hospital, basado en los criterios de eficacia, eficiencia y calidad.

2.5 - Disponer las acciones necesarias para garantizar que el desarrollo del proceso investigador y la gestión del conocimiento se adecuan a los principios éticos, deontológicos y de legalidad vigentes.

Tercera.- Compromisos de las partes

3.1 - El Hospital y la Fundación convienen, de mutuo acuerdo, que la sede social de la Fundación se encuentre en el hospital.

3.2 - Las partes intervinientes acuerdan que el Hospital y la Fundación se hacen cargo, en su conjunto y de manera global, de todas las actividades de promoción, impulso y coordinación de la investigación establecidas en la cláusula 2.1.

Así, la Fundación se compromete gestionar la investigación llevada a cabo por el Hospital o a su iniciativa, desarrollando un modelo de gestión propio, basado en criterios de eficacia, eficiencia y calidad. En consecuencia cualquier proyecto de investigación, incluidos los ensayos clínicos, deberán contar con la autorización del Director Gerente del Centro sanitario.

3.3 - La Fundación impulsará la elaboración de programas y proyectos de investigación, y promoverá su presentación ante las Agencias Públicas de financiación de la investigación, así como ante otras entidades públicas o privadas que destinen recursos financieros a la subvención de programas de investigación.

3.4 - La Fundación fomentará la colaboración con universidades, organismos nacionales e internacionales, empresas del sector biosanitario, de desarrollo tecnológico, del sector farmacéutico, asociaciones y fundaciones de pacientes, así como con otras fundaciones de investigación.

3.5 - La Fundación, dentro de los límites de su actuación, impulsará la realización de ensayos clínicos en el Hospital, de acuerdo con la legislación vigente.

3.6 - La Fundación gestionará los ensayos clínicos que, una vez aprobados por la autoridad sanitaria competente, de acuerdo con la normativa vigente, y por el Comité Ético de Investigación Clínica y la Dirección Medica, se lleven a cabo en el Hospital.

Los contratos correspondientes serán firmados por el Presidente de la Fundación, o persona en quien delegue.

Mediante el contrato entre la Fundación y el promotor del proyecto de investigación se fijarán además las retribuciones que hayan de percibir los investigadores, los costes directos e indirectos, ajustándose a la normativa vigente.

En particular, en lo que se refiere al capítulo económico, el Hospital una vez realizado el servicio emitirá la correspondiente factura a la Fundación que realizará el correspondiente pago con cargo a la cuenta del ensayo de referencia.

3.7 - La Fundación llevará a cabo la gestión económica y administrativa de los fondos recibidos por los investigadores en concepto de becas, ayudas, donaciones, subvenciones, etc. para la financiación de proyectos.

3.8.- La Fundación, con cargo a la cuenta de los proyectos de investigación, podrá abonar al personal del hospital por el desarrollo de su labor los importes que, previamente, sean acordados y siempre bajo cumplimiento de la normativa vigente.

3.9 - La Fundación gestionará contratos, convenios, acuerdos, o cualquier otro tipo de documento contractual con terceros, ya sean instituciones públicas o privadas, empresas, universidades, organismos nacionales o internacionales, asociaciones, fundaciones, etc.

3.10 - La Fundación podrá ceder al Hospital los equipos y demás material inventariable, que sea adquirido por la misma con cargo a proyectos, estudios o programas financiados por Agencias, entidades de organismos públicos, así como cuando siendo financiados por entidades de cualquier otro tipo el Investigador Principal del proyecto así lo manifieste. En el caso del material cedido el hospital procederá al mantenimiento del equipamiento cedido.

3.11 - La Fundación tramitará los procedimientos administrativos relativos al registro de patentes y de Propiedad Intelectual.

3.12 - El Hospital, entendiendo que la Fundación es su instrumento para la gestión de la investigación, y para dar cumplimiento a lo previsto en el presente convenio podrá poner a disposición de la Fundación los recursos necesarios, sin perjuicio de los posibles acuerdos de gestión que puedan suscribirse entre las partes (Hospital/Fundación).

3.13 - El Hospital se compromete a reconocer funcionalmente, a los becarios adscritos a proyectos y a los investigadores que serán contratados por la Fundación, como asimilados al personal de servicio del Hospital, a los solos efectos de que puedan figurar como investigadores principales en la solicitud de convocatorias de proyectos y ayudas a la investigación que sean presentadas ante cualquier tipo de agencia, organismo o entidad, ya sean publicas o privadas.

3.14 - En cualquier caso el reconocimiento funcional del personal de la Fundación, no comportará el establecimiento de ningún tipo de vínculo contractual, ni supondrá ninguna obligación del Hospital con respecto a dicho personal. Por lo tanto el Hospital no asume ninguna responsabilidad en materia contractual, laboral, estatutaria ó administrativa con el personal laboral o becario contratado por la Fundación.

3.15 - Ambas partes se comprometen a realizar las gestiones oportunas ante las autoridades competentes para que todos los ingresos procedentes de investigación tengan la consideración de finalistas mediante la generación de los correspondientes créditos, del mismo modo que se ha llevado a cabo con ocasión de las Redes Temáticas de Investigación Cooperativa.

Cuarta.- Modificación y resolución.

4.1- Este convenio podrá ser modificado de mutuo acuerdo de las partes, cuando éstas lo consideren oportuno.

4.2- Serán causas de resolución del mismo:

a) El mutuo acuerdo de las partes.
b) La denuncia de una de las partes formulada con tres meses de antelación.
c) La imposibilidad de su cumplimiento por causas sobrevenidas ajenas a las partes.

Quinta.- Criterios de interpretación y resolución de conflictos.

Las diferencias que pudieran surgir en la interpretación de las cláusulas de este convenio, y que no puedan ser resueltas en el marco bilateral entre el Hospital y la Fundación, se someterán al arbitraje previsto en la Ley 60/2003, de 23 de diciembre, sobre Arbitraje, el nombramiento del arbitro recaerá sobre la persona que, de común acuerdo, designen las partes implicadas, a falta de acuerdo, la designación la realizará la Dirección General de la Agencia Pedro Laín Entralgo.

Sexta.- Vigencia del Convenio.

El presente convenio entrará en vigor en el momento de su firma, teniendo vigencia indefinida, sin perjuicio de lo establecido en la cláusula cuarta respecto a su modificación o resolución.

Y en prueba de conformidad del contenido del presente convenio, se firma el presente por triplicado y a un solo efecto, en el lugar y fecha arriba indicado.

El Presidente de la Fundación para la Investigación Biomédica del Hospital Universitario Puerta de Hierro

Javier Carro González

El Director General del Instituto Madrileño de la Salud

Jorge Tapia Sáez

Attachment 6: Form Cs Summary

FP7 - Grant Agreement - Annex VI - Collaborative project

Summary Financial Report - Collaborative project

Project acronym	REBORNE	Project nr.	241879	Reporting period from	01/01/2010	to	31/12/2010	Page	1/1

Funding scheme	CP

Beneficiary nr.	If 3rd Party, linked to beneficiary	Adjustment (Yes/No)	Organization Short Name	Type of activity								Total (A)+(B)+(C)+(D)		Receipts	Interest
				RTD (A)		Demonstration (B)		Management (C)		Other (D)					
				Total	Max EU Contribution	Total	Max EU Contribution	Total	Max EU Contribution	Total	Max EU Contribution	Total	Max EU Contribution		
1		No	INSERM	226,102.74	169,577.06	0.00	0.00	110,285.17	110,285.17	0.00	0.00	336,387.91	279,862.23	0.00	0.00
	1	No	UNIVERSITE DE NANTES	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2		No	EFS	490,866.14	368,149.61	0.00	0.00	0.00	0.00	0.00	0.00	490,866.14	368,149.61	0.00	0.00
3		No	BIOMATLANTE	99,724.24	74,793.18	0.00	0.00	0.00	0.00	0.00	0.00	99,724.24	74,793.18	0.00	0.00
4		No	CEA	11,675.69	8,756.77	0.00	0.00	0.00	0.00	0.00	0.00	11,675.69	8,756.77	0.00	0.00
5		No	POLICLINICO	154,062.89	115,547.17	0.00	0.00	0.00	0.00	7,920.00	7,920.00	161,982.89	123,467.17	0.00	0.00
6		No	CHU NANTES	72,004.19	54,003.14	0.00	0.00	0.00	0.00	2,192.45	2,192.45	74,196.64	56,195.59	0.00	0.00
7		No	AP-HP	39,144.27	29,358.20	0.00	0.00	0.00	0.00	0.00	0.00	39,144.27	29,358.20	0.00	0.00
8		No	KITO	76,698.34	57,523.76	0.00	0.00	0.00	0.00	0.00	0.00	76,698.34	57,523.76	0.00	0.00
9		No	XPAND	176,363.18	132,272.39	0.00	0.00	0.00	0.00	0.00	0.00	176,363.18	132,272.39	0.00	0.00
10		No	UPC	151,056.16	113,292.12	0.00	0.00	0.00	0.00	4,524.07	4,524.07	155,580.23	117,816.19	0.00	0.00
11		No	UAM	78,009.44	58,507.08	0.00	0.00	0.00	0.00	0.00	0.00	78,009.44	58,507.08	0.00	0.00
	11	No	SERVICIO MADRILEÑO DE SALUD	21,464.24	16,098.18	0.00	0.00	0.00	0.00	0.00	0.00	21,464.24	16,098.18	0.00	0.00
12		No	UNIMORE	191,963.23	143,972.42	0.00	0.00	0.00	0.00	7,328.64	7,328.64	199,291.87	151,301.06	0.00	0.00
13		No	UMFTVB	1,462.56	1,096.92	0.00	0.00	0.00	0.00	36,382.94	36,382.94	37,845.50	37,479.86	0.00	0.00
14		No	CHU TOURS	1,972.42	1,479.32	0.00	0.00	0.00	0.00	0.00	0.00	1,972.42	1,479.32	0.00	0.00
15		No	UNITUE	138,536.43	103,902.32	0.00	0.00	0.00	0.00	0.00	0.00	138,536.43	103,902.32	0.00	0.00
16		No	UULM	201,669.52	151,252.14	0.00	0.00	0.00	0.00	0.00	0.00	201,669.52	151,252.14	0.00	0.00
17		No	UNIVR	80,696.54	60,522.41	0.00	0.00	0.00	0.00	0.00	0.00	80,696.54	60,522.41	0.00	0.00
18		No	ALCIMED	0.00	0.00	0.00	0.00	89,316.98	89,316.98	10,475.13	10,475.13	99,792.11	99,792.11	0.00	0.00
19		No	UiB	45,381.36	34,036.02	0.00	0.00	0.00	0.00	0.00	0.00	45,381.36	34,036.02	0.00	0.00
20		No	UMC UTRECHT	8,450.74	6,338.06	0.00	0.00	0.00	0.00	0.00	0.00	8,450.74	6,338.06	0.00	0.00
21		No	IOR	19,324.56	14,493.42	0.00	0.00	0.00	0.00	0.00	0.00	19,324.56	14,493.42	0.00	0.00
22		No	MPG	186,577.20	139,932.90	0.00	0.00	0.00	0.00	0.00	0.00	186,577.20	139,932.90	0.00	0.00
23		No	AOU MEYER	14,208.00	10,656.00	0.00	0.00	0.00	0.00	0.00	0.00	14,208.00	10,656.00	0.00	0.00
24		No	ULG – PARO	4,875.79	3,656.84	0.00	0.00	0.00	0.00	0.00	0.00	4,875.79	3,656.84	0.00	0.00
TOTAL				2,492,289.87	1,869,217.43	0.00	0.00	199,602.15	199,602.15	68,823.23	68,823.23	2,760,715.25	2,137,642.81	0.00	0.00

Requested EU contribution for the reporting period (in €)	2,137,642.81