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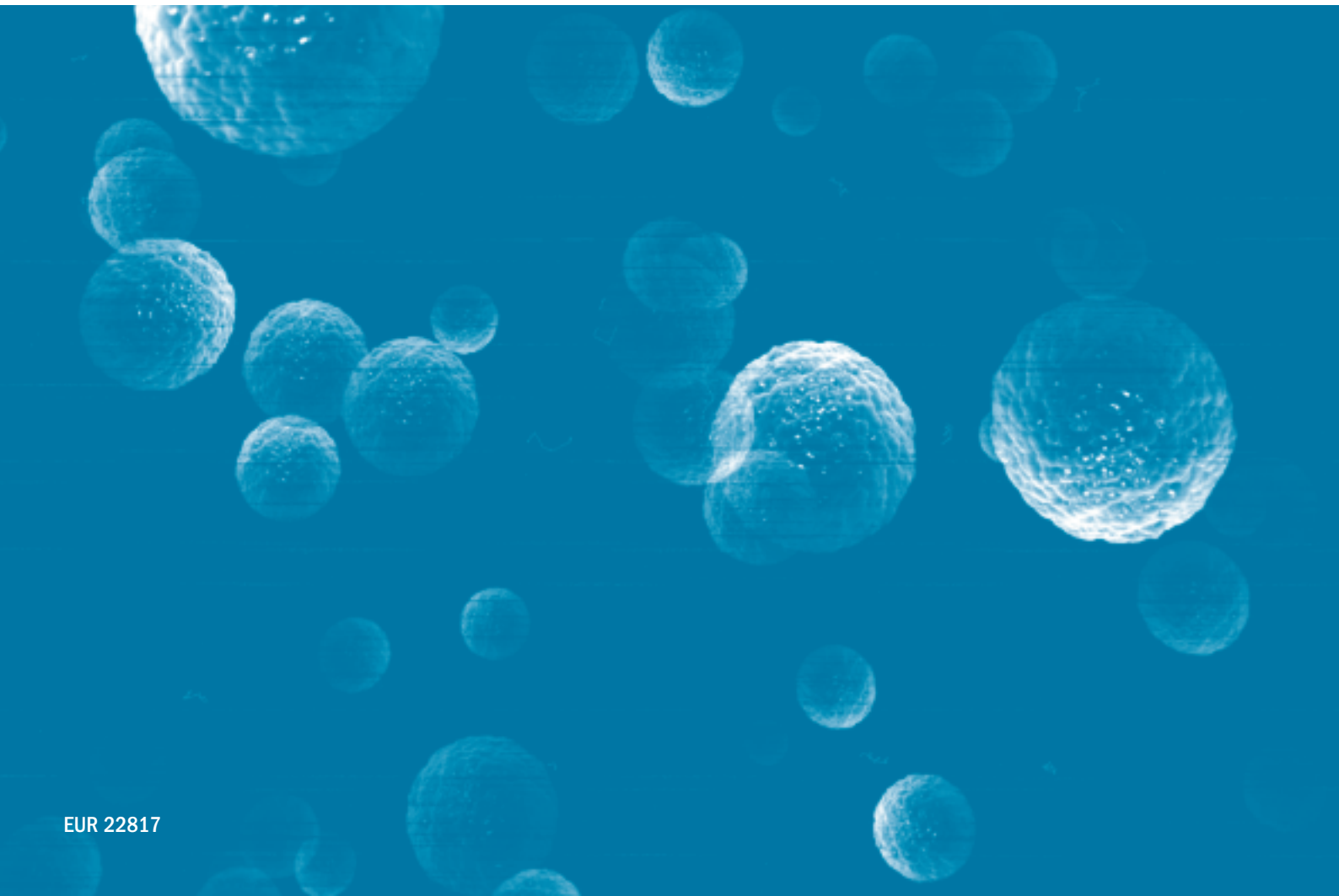
A decade of EU-funded research



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BIOMATERIALS FOR HEALTHCARE
A decade of EU-funded research

T. F. Larsson, J. M. Martín Martínez and J. L. Vallés

2007

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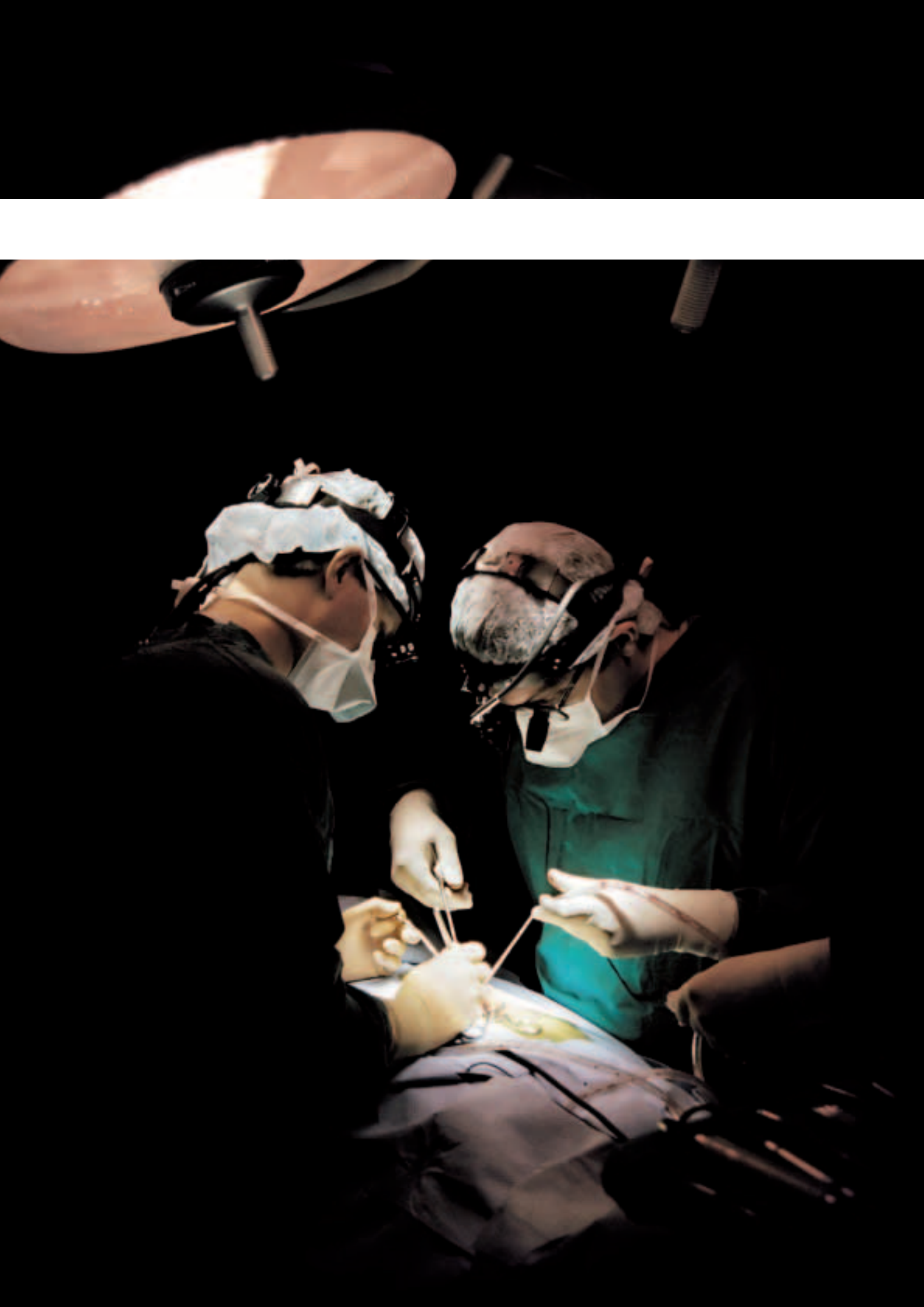


At the leading edge of medicine

Biomaterials are materials with novel properties that make them especially suitable to have an intimate contact with living tissue, and are produced through processes that often employ or mimic biological phenomena.

Biomaterials are revolutionising many aspects of preventive and therapeutic healthcare. They are already playing an important role in the development of new medical devices, prostheses, tissue repair and replacement technologies, drug delivery systems and diagnostic techniques.

With huge potential quality-of-life benefits for all, biomaterials are the focus of major research efforts around the world. Progress in this field requires a multidisciplinary approach, where scientists (chemists, physicists, mathematicians, biologists and medical doctors), interact with engineers, materials producers and manufacturers.

Moreover, the nature of the challenges is such that finding solutions often demands an investment of skills and resources that are beyond the capabilities of a single organisation, or even of a single country. Collaborative research is thus the key to achieving breakthrough results likely to bring leadership in the global marketplace.

The European Union (EU) has funded biomaterials research projects (RTD) under its Fifth and Sixth Framework Programmes for almost a decade. The following pages trace the progress of this work, illustrated by examples of projects that have achieved significant advances or highlighted fruitful areas for continuing investigation.

Biomaterials research: an evolving field

Because biomaterials for medical applications are intended to be in contact with the human body, they must be biocompatible, and either bioresorbable (soluble sutures, bone and cartilage,…) or biodurable (orthopaedic implants, bone grafts, coronary stents…).

Technologies in this field have advanced through three broad generations:

1. bioinert materials;
2. bioactive materials (including surface coatings) which encourage the regeneration of natural tissue;
3. intelligent, adaptive systems able to favour angiogenesis (the development of new blood vessels) in regenerated tissue by combining at least two different types of cell, and producing their own extra-cellular matrices.

Main issues

The critical issues to be addressed in biomaterials research include:

1. lack of knowledge of the fundamentals of the **interfacial interactions**;
2. need to establish **relationships between the molecular structures and properties** of biomaterials;
3. lack of technology for the **controlled conversion of biomacromolecules** into an hierarchical structure;
4. development of **biomaterials for particular diseases** – cardiovascular, diabetes 1, hepatitis, arthritis, osteoporosis, etc;
5. serious **limitations of existing tissue bioadhesives** (synthetic, biological, genetically engineered) and medical adhesives for wound closure, internal organs and prostheses.

Today, nanotechnologies and inorganic-organic hybrid technologies are regarded as important tools to be deployed in solving these problems.

The EU role in biomaterials research

EU support for biomaterials research within the two latest Framework Programmes began in 1997. Although not named as a topic in its own right under the Fifth Framework Programme (FP5), 38 biomaterials projects were funded, with a total granted amount of €66.6 million.

In FP6, biomaterials issues were selected as a specific topic in three calls for proposals under Priority 3 (NMP).

1st Call:

- Molecular and bio-molecular mechanisms and engines;
- Interfaces between biological and non-biological systems;
- Tissue engineering, new biomimetic and biohybrid systems.

2nd Call:

- Molecular motors;
- Nanostructured surfaces;
- 'Intelligent' biomaterials for tissue repair and regeneration;
- Materials by design: bio-inspired materials and organic-inorganic hybrid materials.

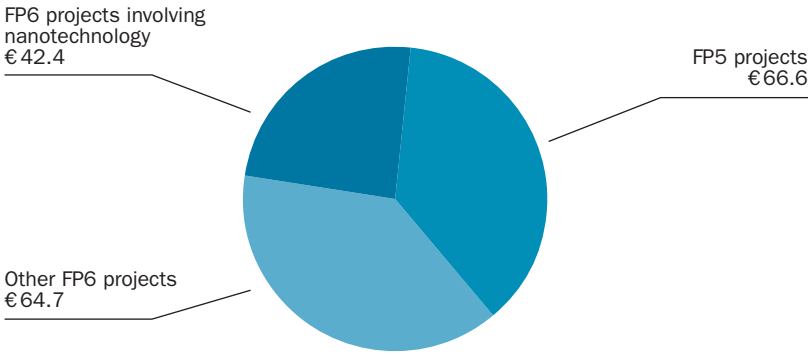
3rd Call:

- Nanotechnology-based targeted drug delivery;
- Biomaterials technologies for implants.

As a result, 36 projects specifically devoted to biomaterials have been funded under Priority 3, with a total granted amount of €107.1 million.

Thus, under FP5 and FP6 the EU has funded biomaterials research by a total of €173.7 million.

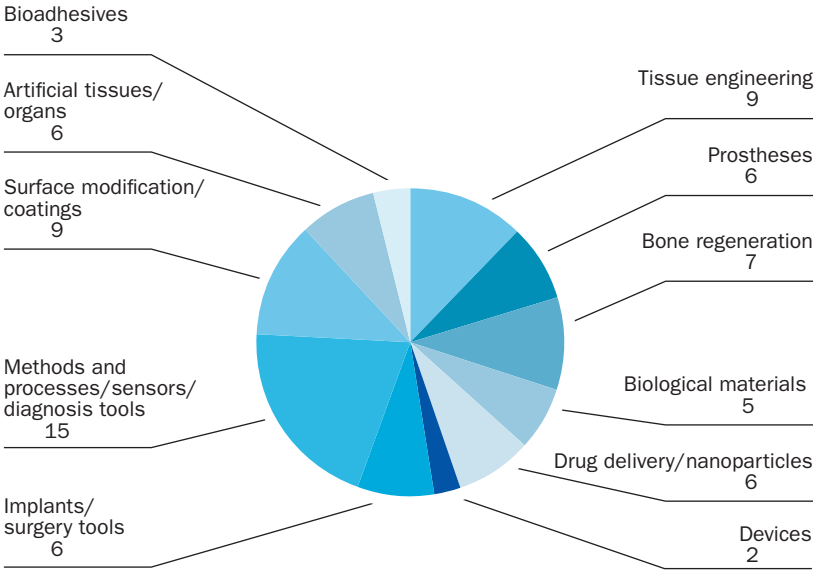
Distribution of funded projects



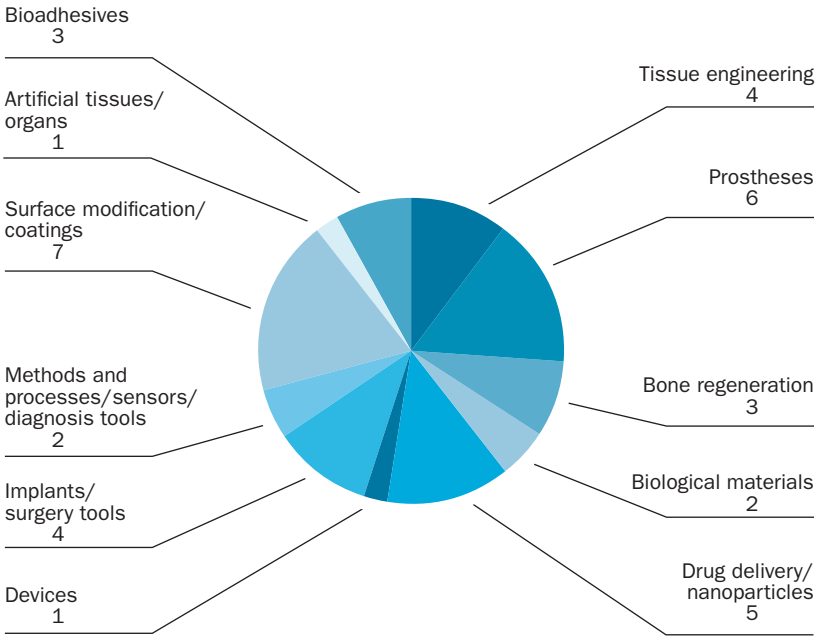
Changing focus

Several topics – including tissue engineering, bone regeneration and drug delivery – were funded in both FP5 and FP6. However, some topics funded under FP5 (prostheses/implants, surface coatings, bioadhesives) were not explicitly retained in FP6. Conversely, FP6 did address the new fields of artificial tissues and sensors.

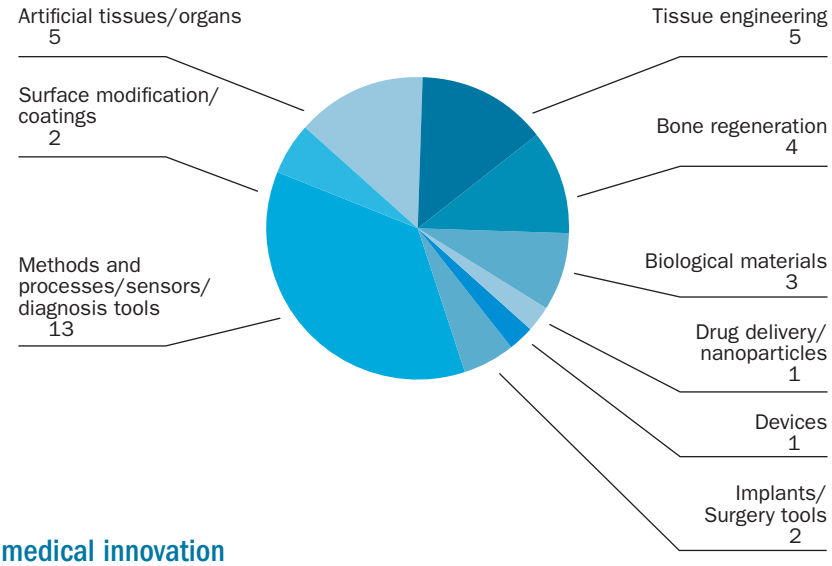
Total number of projects in FP5 and FP6 per topic (€ 173.7 million)



Total number of projects in FP5 per topic (€ 66.6 million)



Total number of projects in FP6 per topic (€ 107.1 million)



Driving medical innovation

Projects funded by the EU appear to align closely with the trends of evolution in the biomaterials industry itself. Technologies for prostheses/implants and surface coatings are already well advanced in the marketplace. Current research interest focuses principally on tissue engineering, bone repair, diagnostic tools and medical adhesives.

Biomaterials in FP5

Distribution of projects funded by EU in biomaterials (FP5)

Instrument	Number of projects	EC funding
RD	27	€60.4 million
CR	10	€5.7 million
TN	1	€0.5 million
TOTAL	38	€66.6 million

RD = Research and Development (GROWTH) project;
CR = Cooperative Research (CRAFT) project;
MC = Acompanying Measurements;
NAS = RD projects involving new incoming countries.

The 38 granted projects can be grouped into the following topics :

- Tissue engineering
- Prostheses
- Bone regeneration
- Biological materials
- Drug delivery/nanoparticles
- Implants/surgery tools
- Methods and processes/sensors/diagnosis tools
- Surface modification/coatings
- Artificial tissues/organs
- Bioadhesives

Novel technologies for soft tissue reconstruction (2000-2004)

Existing methods for regeneration of soft-tissue – by transplantation, or using alloplastic materials (which adapt by altering their external environments) or fillers – were unsatisfactory. Problems included limited resorbtion, shrinkage, degradation and adverse immune response.

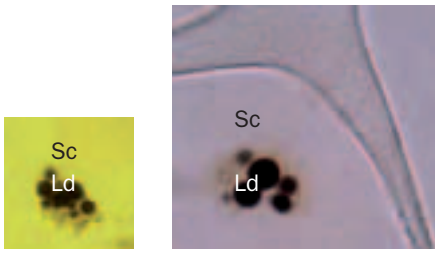
ADIPO-REGENERATION set out to pursue an approach employing tissue regeneration, rather than tissue repair, based on:

- laboratory-growth of functioning cells and tissues derived from patient biopsies;
- production of synthetic polymers to elicit specific cellular functions and serve as scaffolds for cells.

Project successes

1. Two tissue engineered scaffolds made of biopolymers based on hyaluronic acid (HYA), in the form of an implantable pre-formed scaffold and an injectable gel were prepared.

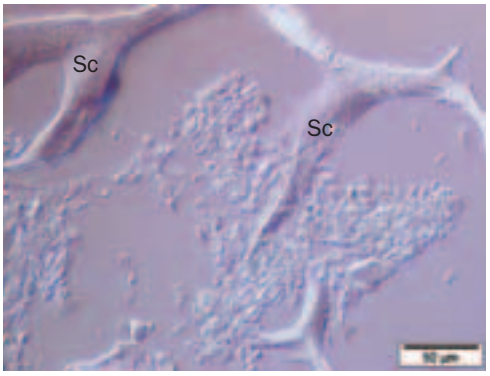
Hyaluronic acid sponge designed for autologous adipose tissue regeneration in a pig model.



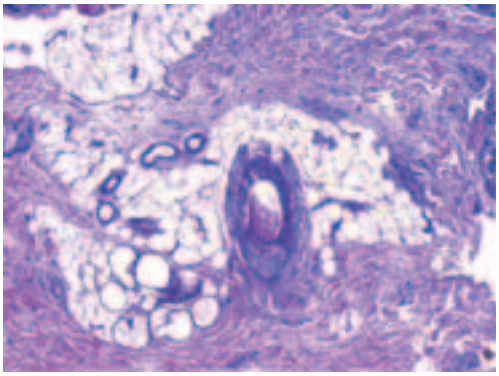
In-vitro 3D differentiation of preadipocytes into mature adipocytes on spongy scaffolds. Osmium tetroxide staining.

Sc = scaffold;
Ld = Lipid droplets accumulating in the cytoplasm.

2. HYA-based biopolymers shown to act as a delivery vehicle that is biodegradable, can be seeded with adipocyte precursor cells, and promotes neovascularisation.



Inverse contrast microscopy of preadipocyte-inoculated hyaluronic acid sponge, three days after seeding.



Neovascularisation and presence of adipose tissue in preadipocyte-seeded hyaluronic acid gel injected in the pig ear. Six weeks in vivo. Haematossilin eosin staining.

G5RD-CT-1999-00111 – ADIPO-REGENERATION
Novel technologies for soft tissue reconstruction: a tissue engineering solution based on biocompatible polymers and adipocytes-precursors cells.

Total cost
€2 520 500
EC contribution: €1 750 673

Project duration
January 2000 – December 2004 (60 months)

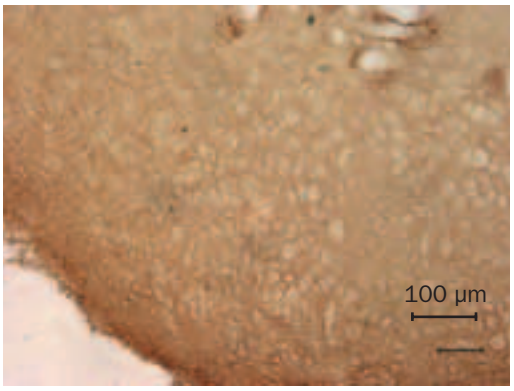
Coordinator
Cristina Martellozo – Fidia Advanced Biopolymers srl, Abano Terme, Italy

Effective repair of arthritic joints (2000-2004)

Osteoarthritis, or degenerative joint disease, currently affects 20 million European citizens, while over 3 million new cases arise per year worldwide. The disease causes excruciating pain and, ultimately, loss of joint function.

The objectives of SCAFCART were to:

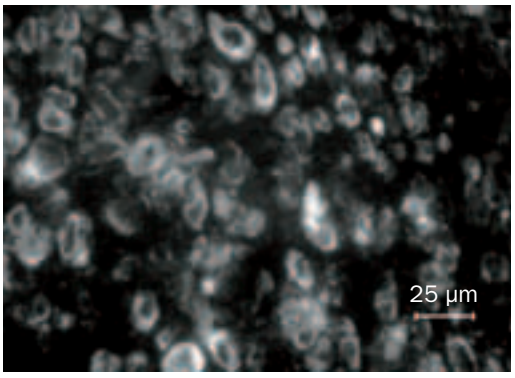
- optimise tissue engineering scaffolds for repair of defects in human articular cartilage;
- improve methods for the culture of chondrocyte-scaffold constructs and osteochondral constructs for surgical delivery;
- devise new approaches for integrating cell-material constructs with local host tissues (articular cartilage and bone) at the surgical site.



Type II collagen (stained brown) in the extracellular matrix of the construct.

Project successes

1. Development of a novel in-vitro model system based on hyaluric acid (HYA) to generate cartilage. By loading half of the cells on each side of the scaffold and inverting it at hourly intervals, a particularly even cell distribution was achieved.
2. Development of a functional bioreactor for cyclic loading of cartilage in osteochondral composite tissue.
3. Demonstration that a chondron unit (a cartilage cell plus a specialised pericellular matrix rich in type VI collagen) is essential for the appropriate response of the cartilage cell to mechanical loading and other extracellular stimuli.



Collagen rich area showing chondrons.

G5RD-CT-1999-00050 – SCAFCART
Novel bioresorbable scaffolds and culture methods for cartilage tissue engineering.

Total cost
€6 098 611
EC contribution: €2 984 379

Project duration
January 2000 – December 2004 (60 months)

Coordinator
Paul Hatton – University of Sheffield, School of Clinical Dentistry, Sheffield, United Kingdom

Spinal inserts relieve lower back pain (2001-2005)

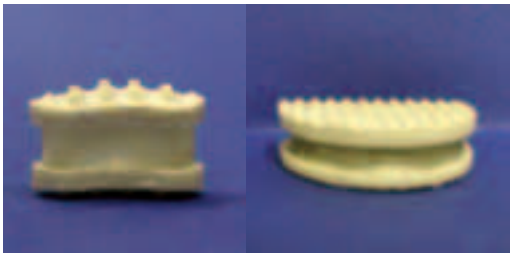
Low back pain is a common problem in industrialised countries. Currently available artificial disc implants for the spine are less than ideal, because they require complex surgical procedures for placement, and are prone to wear and degeneration.

In project DISC, the goals were to:

- reduce implant failure rates;
- increase biocompatibility;
- minimise surgery time and costs.

Project successes

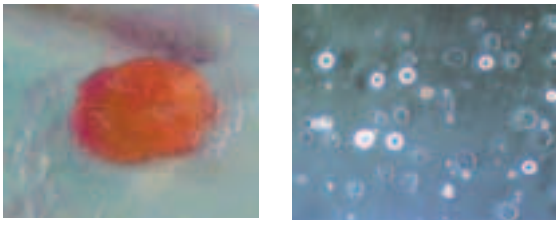
1. Development of acellular injectable nucleus substitute materials made of hyaluric acid (HYA) and polyethylene glycol-based polymers.
2. Production of a cell-loaded nucleus material [poly(ethylene glycol) vinyl sulphone-peptide hydrogel], which is injectable, biocompatible, and biodegradable.
3. Design of a disc model consisting of two artificial end-plates.



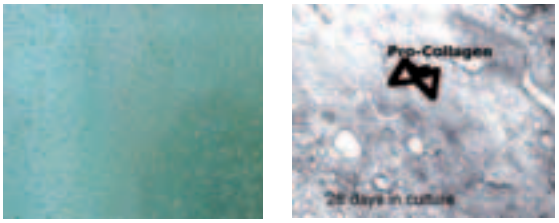
For pig *For human*

Two artificial end-plates made of HYA-reinforced polyethylene and a composite hydrogel (PHEMA/PMMA (polyhydroethyl metacrylate/polymethylmetacrylate) semi-interpenetrating network reinforced by helically wound treated polyethyleneterephthalate fibres).

4. Isolation and culturing technique for marrow stem cells.



Marrow stem cells into HYA-based gel.



Bone marrow stem cells in PEG-peptide gels. Adhesion and proliferation of marrow stem cells showing ability to express chondrogenic proteins.
14 days in culture (left picture)
28 days in culture and Pro-collagen (right picture)

G5RD-CT-2000-00267 – DISC
Novel disc intervertebral prostheses.

Total cost
€5 696 674
EC contribution: €2 884 096

Project duration
January 2001 – July 2005 (54 months)

Coordinator
Luigi Ambrosio – National Research Council of Italy, Istituto per i Materiali Compositi e Biomedici, Naples, Italy

Gaining ground in bone substitute production (2001-2004)

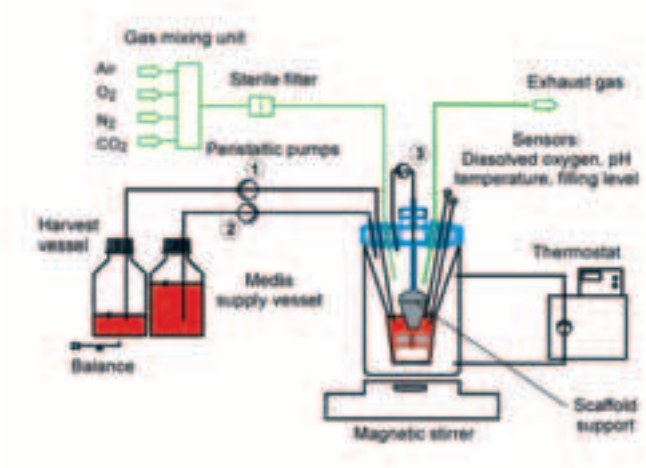
With Europe lagging behind the US in bone substitution products, there was a need to combine novel technology and strategies to develop innovative processes for the production of engineered vascular bone tissue in the EU.

The aims of the project TISSUE REACTOR were to:

- develop both materials and a production methodology;
- establish in-vitro cell culture protocols to expand rabbit and human dynamic 3D bone cultures;
- develop in-vitro rabbit endothelial cell culture system that can be invaded by a capillary-like precursor for a vascular system.

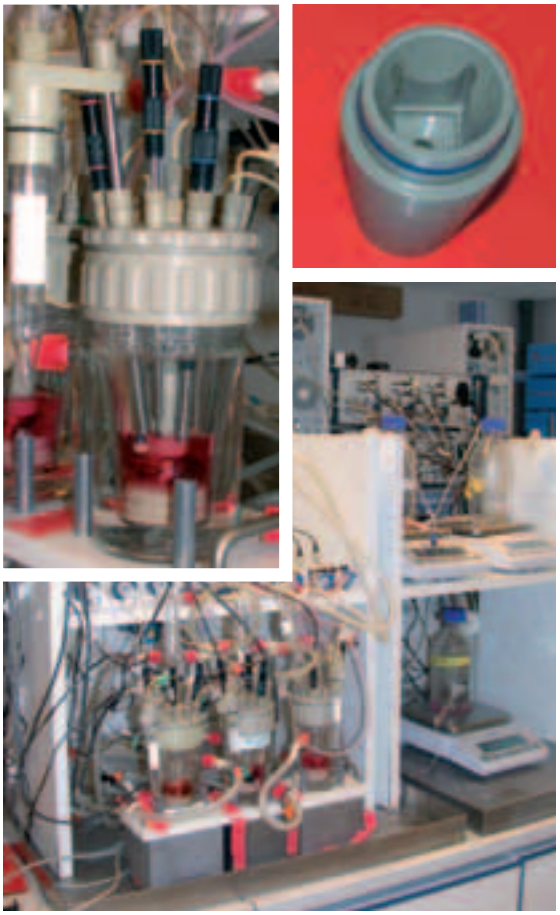
Project successes

1. Biodegradable macroporous scaffolds with interconnective pore structure based on CaP-ceramic or PLGA polymer with hydroxyapatite (HA) nanoparticles, suitable as initial primer structures for 3D bone cultures.
2. A non-destructive sterilisation method for the scaffolds.
3. Tailored perfluorocarbon (PFC) emulsion media for improved in-vitro oxygenation of 3D bone cultures in fixed-bed bioreactors.
4. A continuously perfused fixed-bed bioreactor system for the production of the 3D bone cultures, endothelial cell cultures and co-cultures between them.



Set-up of the bioreactor system

As well as improving the clinical situation in bone substitution surgery, this valuable contribution to the field of bioreactor-based cell culture technology could provide a powerful tool for other forms of tissue engineering.



G5RD-CT-2000-00282 – TISSUE REACTOR
Development of a bioreactor-based connective issue production line.

Total cost
€2 881 000
EC contribution: €2 381 000

Project duration
January 2001 – December 2004 (48 months)

Coordinator
Ralf-Peter Franke – University of Ulm, Ulm, Germany

Making the most of a natural rejuvenator (2003-2005)

Extracts from the berries of sea buckthorn, a plant growing in the mountainous regions of China and Russia, are employed mainly in the production of vitamin C-containing juice. To date, other by-products of the fruit have remained relatively under-utilised. Recently, however, several products containing pulp and seed oil have appeared as cosmetic formulations and nutritional additives.

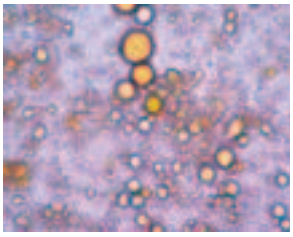
A particularly interesting property is the ability to promote regeneration of the skin, mainly due to high beta-carotene content. This can be exploited in the treatment of burns, poorly healing wounds and skin ulcers. Moreover, since the berries contain antioxidants, they combat wrinkles, dryness, the symptoms of ageing and skin neglect.

Because the oil suffers from light instability, proneness to oxidation and poor low temperature resistance, the SEABUCK project sought to design a process for extracting carotenoid-lipoprotein complexes from the fruit pulp, which contains most of the valuable health-promoting components. Its goals were to:

- produce the carotenoid-lipoprotein complex (CLP) on a commercial scale, and to devise a strategy and technology scheme for use of the entire sea buckthorn fruits, reducing the low-value by-products to a minimum;
- develop and produce innovative cosmetic formulations containing CLP.

Project successes

1. Identification of the parameters influencing yield and stability (temperature, time, pH).
2. Identification of the requirements for harvest, transportation and processing of the berries.
3. Technology for extraction, separation and purification of the CLP at laboratory, pilot and full scale (enzymatic and heat treatment).
4. Analysis of the chemical composition and the stability of the CLP-containing sea buckthorn fraction, indicating positive anti-oxidative and regenerative skin-care effects resulting from the high content of carotenoids, unsaturated fatty acids and proteins in a bio-available hydro-colloidal form.



Microscopic view of CLP- rich oil vesicles from sea buckthorn pulp.

Sun body lotion containing 1% CLP from sea buckthorn Jam containing 50% sea buckthorn butter.

G5ST-CT-2002-50352 – SEABUCK
Innovative products obtained from fruits of sea buckthorn.

Total cost
€537 100
EC contribution: €268 500

Project duration
March 2003 – February 2005 (24 months)

Coordinator
Eike Doepelheuer – Kroppenstedter Olmuhle Walter Dopelheuer gmbh, Koppenstedt, Germany

Magnetic particles permit targeted medication (2001-2003)

Small particles containing biologically active molecules and radioactive markers have been used for 40 years in in-vitro diagnostics. Over the past decade, nano-sized magnetic particles have been developed. These can be directed to a particular site by using magnets positioned outside a patient's body, but their potential for cell targeting was limited due to low binding capacity.

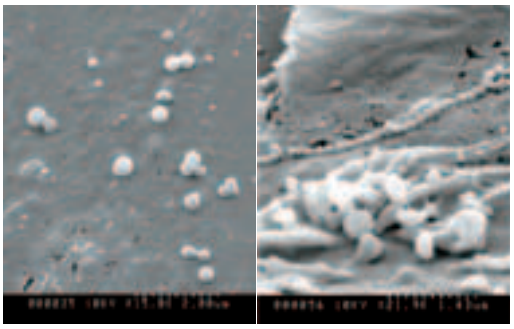
Magnetic nanoparticles combining a magnetic core with a shell layer possessing the desired properties for functionalisation would solve this problem. They would greatly facilitate the precise delivery of anti-inflammatory drugs or other medication to an exact area of tissue, thereby reducing dosage errors, eliminating side effects and achieving faster treatment.

The aims of the MAGNANOMED project were to develop:

- new types of nanoparticles of specific shape and precise size, with tailored surface chemistry and topography for biomedical purposes;
- treatment of auto-immune diseases by direct delivery of immunosuppressive drugs to the musculo-skeletal system.

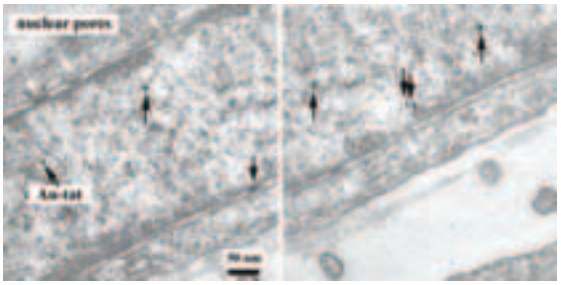
Project successes

1. Manufacture of superparamagnetic nano-sized particles suitable for coating and functionalisation with proteins. Particles with different shapes (spheres, needle-like) and high aspect ratios (>5) were obtained.

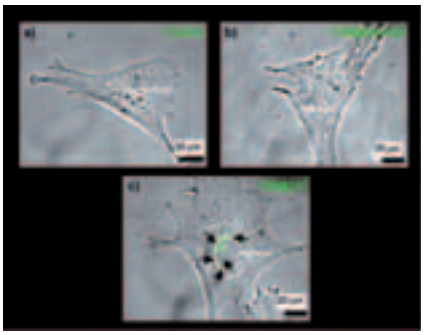


Nanoparticles (left) and transferrin attachment (right) on surface.

2. Testing to determine the liability of the nanoparticles to become phagocytosed or to induce necrosis and/or apoptosis; plus monitoring of cell adhesion changes.



Nanoparticles delivered into cell nuclei.



Distribution of nanoparticles in tissue.

G5RD-CT-2000-00375 – MAGNANOMED
Magnetic nanoparticles for medical and biological diagnostics and devices.

Total cost
€3 377 137
EC contribution: €2 394 000

Project duration
January 2001 – December 2003 (36 months)

Coordinator
Adam Curtis – University of Glasgow, Institute of Biomedical and Life Sciences, Glasgow, United Kingdom

Computer-modelled drug system reduces heart treatment risk (2001-2005)

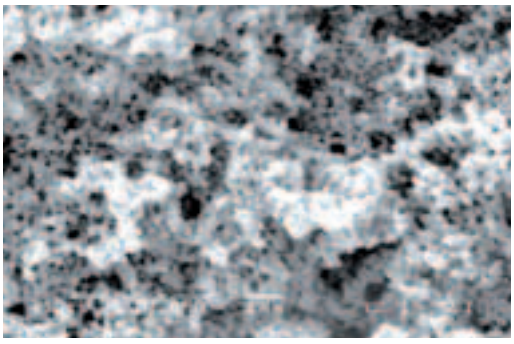
Coagulation in the vascular system – particularly intracoronary thrombus – is the cause of 95% of acute myocardial infarction, or 'heart attacks'. The use of conventional thrombolytic drugs to dissolve clots can give rise to severe haemorrhages. This can be avoided by the use of fibrin-targeted plasminogen formulations, since fibrin accelerates activation of the plasminogen. Furthermore, localising their delivery would allow very high concentrations of drugs to be used – thus increasing the bioavailability, giving a rapid dissolution of the thrombus and avoiding circulating overload.

In its bid to respond to this challenge, the TATLYS project covered three main areas:

- computer modelling of the 3D structure of fibrin epitopes and the corresponding paratopes responsible for binding;
- scaled-up production of polymers for nanoparticle fabrication, monoclonal antibody, fibrin paratope, and drug-loaded targeted nanoparticles, plus assessment of their stability;
- in-vitro and in-vivo evaluation of the activity of the drug released from nanoparticles, and of the toxicity of the drug-loaded nanoparticles and their individual components.

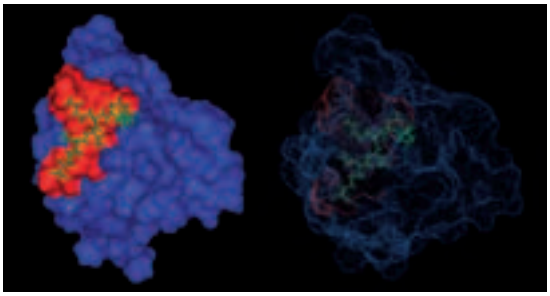
Project successes

1. Development and scaled-up production of biocompatible hemiesters of methoxy ethanol of alkyl vinylether/anhydride alternating copolymers grafted with 5% methoxy polyethylene glycol (PEG) 2000.
2. Production of nanopolymers of 3-hydroxybutyric acid by novel anionic polymerisation in polar solvents, displaying a monomodal size distribution and an average size of 120-130 nm.



SEM micrograph of biofunctionalised grafted nanoparticles. Average diameter 120±16 nm.

3. Preparation of magnetic fluids containing magnetite particles. These particles can be coated with dextran and poly(ethylene glycol) (PEG) or with oligopeptides (fibrin epitopes, paratopes).
4. In-vitro experiments indicating that the introduction of PEG can bring a significant decrease in cytotoxicity.
5. Development of a computer model of the 3D structure of fibrin epitopes.



Computer model of 3D structure of fibrin epitopes.

G5RD-CT-2000-00294 – TATLYS
A new biocompatible nanoparticle delivery system for targeted release of fibrinolytic drugs.

Total cost
€3 996 748
EC contribution: €2 224 269

Project duration
February 2001 – January 2005 (48 months)

Coordinator
Emo Chiellini – INSTM – Consorzio Interuniversitario Nazionale per la Scienza e Tecnologia dei Materiali, Department of Chemistry and Industrial Chemistry, Pisa, Italy

Coated catheters for infection-free dialysis implants (2001-2005)

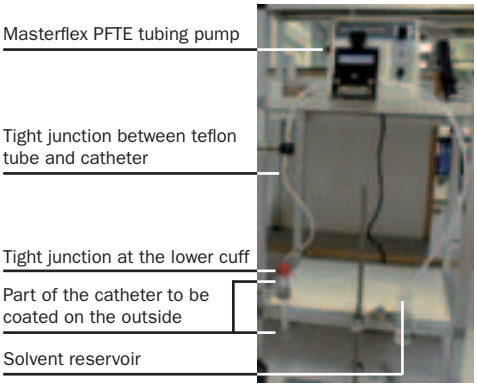
Peritoneal dialysis (PD) is the preferred dialysis method for the treatment of kidney failure. In 2002, the technique was used on 1.2 million people in Europe. Two thirds of all patients admitted to hospital will have an intracorporal PD device inserted for this purpose.

Because the treatment can be carried out by the sufferers themselves, without need to visit a special centre, patient safety in an uncontrolled environment is an especially important issue. But there is a risk that the insert can cause systemic bacterial infections of the skin at the exit site of the catheter – treatment of which costs some €50 million per year.

In the ADHESTOP project, the partners sought to develop a biomimetic surface coating treatment for PD catheters, in order to prevent the occurrence of such infection.

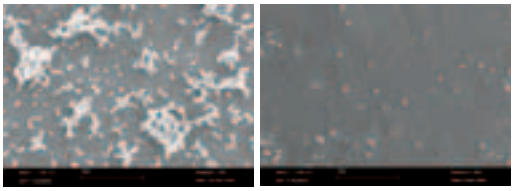
Project successes

1. Production of tetraetherlipid (TEL) through extraction with organic solvents after cultivation and isolation from cells of the patient. Acid hydrolysis of the TEL gave Caldarchaeol. Both TEL and Caldarchaeol were further modified, to yield specifically-ended molecules that could be bonded covalently to surfaces.
2. Development of lab-scale processes based on wet chemistry and self-assembly, for coating silicon surfaces with TEL, using reference materials for comparison.
3. In-vitro testing of material adhesion on TEL layers under real and simulated environmental conditions, together with testing for toxicity. The dynamic testing involved use of a bioreactor.



Lab-scale prototype of a coating system established for catheter application.

4. Evaluation of antibacterial coatings by adhesion models. The roughness of the surface was taken into consideration by adding geometrically regular asperities (projections), which were shown to reduce adhesion. Models were produced for the prediction of antiadhesive and antimicrobial performance of TEL coatings, as well as for the description of adhesion behaviour of bacteria onto patterned surfaces in aqueous media.



Biofilms on uncoated model surface (left) and tetraetherlipid-coated model surface (right).

5. Scale-up of the industrial process for catheter tube manufacture, based on new specific procedures and medical polymers, to produce prototype catheters with integrated antibacterial coating.

Catheter system used for peritoneal dialysis.

G5RD-CT-2001-00594 – ADHESTOP
Biocompatible surfaces to minimise medical device associated infections.

Total cost
€1 690 309
EC contribution: €1 134 732

Project duration
December 2001 – April 2005 (42 months)

Coordinator
Klaus Liefeith – Institute for Bioprocess and Analytical Measurement Techniques e.v., Department of Biomaterials, Heilbad Heiligenstadt, Germany

Fast, computer assisted process delivers made-to-fit bone implants (2001-2004)

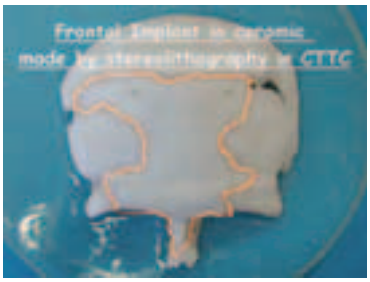
Some 3600 procedures for cranial and facial bone replacement are carried out annually in Europe, to treat cases that can be solved with existing surgical techniques. Patients needing repair of large, irregularly shaped defects are less fortunate. These cannot currently be addressed, but would represent a further 1500 potential operations within the EU region.

Bone tissue replacement operations for cranioplastic and maxillofacial applications are inhibited by a lack of suitable implants with long-term biocompatibility. Currently, the missing bone part is replaced by an autograft or by an implant made manually out of biocompatible polymethyl methacrylate (PMMA) cement. These techniques are unsatisfactory because of an increased risk of infection and of an unaesthetic result. There is increasing demand from surgeons for a business service to supply customised biocompatible ceramic implants fabricated directly from CT scan data, which should be deliverable at affordable cost and with acceptable lead times.

BIOCERARP project explored the development of a prototyping system based on stereolithography, for rapid manufacturing of such parts from 3D computer files. The proposal was to adopt a classical layer-by-layer build-up technique, but to use a high-viscosity paste. For this purpose, prototype software integrating new algorithms was required.

Project successes

1. Identification of one hydroxyapatite powder and one ß tricalcium phosphate powder suitable for stereolithography process.
2. Demonstration that hydroxyapatite parts manufactured with the stereolithographic process show good biocompatibility and appear osteoconductive; they are neither toxic nor mutagenic, and do not induce delayed sensitisation.
3. Implantation of complex-shaped ceramic parts into a sheep skull.
4. Confirmation that implants for distal femoral spongious bone defect show no visible local intolerance, and exhibit excellent osteointegration and osteoconduction properties.



Ceramic frontal implant made by stereolithography.

G5RD-CT-2000-00360 – BIOCERARP

New generation of multi-functional, cost-effective and quick set-up time system for processing and forming ceramic parts dedicated to single or small batch production for medical applications.

Total cost

€1 625 338

EC contribution: €919 806

Project duration

January 2001 – September 2004 (45 months)

Coordinator

Cristophe Chaput – Centre for Technology Transfer in Ceramics, Limoges, France

Plasma sterilization makes medical devices safer (2000-2004)

Today, medical devices are sterilized by various methods that may involve heat, chemicals and ionising radiation. However, there is the need for still more options – especially considering the difficulty of toxicity, and the inability to inactivate endotoxins and prions. Similarly, medical packaging also need sterilization. Plasma sterilization processes could provide a superior and cost-effective answer.

On the other hand, the plastics industry faces increasing environmental concerns regarding flexible PVC-coated devices and plasma processes may be used to develop pre-treatment procedures for plastics of improved coatability and non PVC devices.

The PLASMA PROC/MED DEVICES project sought to investigate plasma processes for sterilization purposes (including medical packaging), and developed biological indicators for validation of their sterilizing effect.

Project successes

1. Demonstration that radio frequency and microwave plasma processes utilising Ar/H_2 and CF_4/O_2 gas mixtures have a biocidal effect on spores.
2. improvement of packaging material properties in terms of peel strength, seal properties, porosity, etc., by using plasma or ozone treatment.
3. Development of non-PVC catheters based on polyethylene/polyurethane materials, and implementation of plasma pre-treatment of polyurethane devices.
4. Coating of hydrophilic polyvinylpyrrolidone (PVP) catheters with monomers such as n-vinyl-2-pyrrolidone.

G5RD-CT-1999-00007 – PLASMA PROC/MED DEVICES
Development of plasma processes for use in cleaner production and sterilization of medical devices.

Total cost
€2 203 544
EC contribution: €1 206 000

Project duration
January 2000 – April 2004 (51 months)

Coordinator
Anne-Lise Hog Lejre – Danish Technological Institute, Materials Technology, Taastrup, Denmark

Meniscus regrowth set to reduce knee replacement demand (2002-2007)

Meniscus defects cause persistent and increasing knee pain, and may lead to osteoarthritis and reduction of mobility. Over 400 000 meniscus injuries are treated in Europe every year.

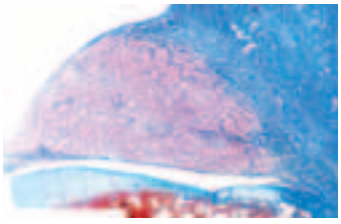
Until recently, the standard repair method was complete resection, likely to result in subsequent injuries to the cruciate ligament and articular joint surfaces, which often make a total knee replacement necessary. A real tissue engineering approach to meniscus reconstruction, involving control techniques for ex-vivo growth of living tissues on 3D Hyaluronan-based scaffolds, would offer a better solution.

In **MENISCUS-REGENERATION**, twin project goals were to:

- develop a novel bioengineered, living meniscus reconstruction material composed of autologous meniscus cells, attached and grown on an optimised biodegradable and bioactive scaffold, for a more efficient treatment of defects;
- design a biocompatible polymeric scaffold that can be degraded and resorbed while triggering differentiation and maturation of articular chondrocytes into meniscus cells (fibrocartilage).

Project successes

1. Selection of culture media and of articular chondrocytes (cartilage cells) containing a high concentration of glycosaminoglycan (GAG) as candidate cell sources for full meniscus regeneration.
2. Analysis of the efficiency with which seeding of meniscus-shaped scaffolds with articular chondrocytes led to the formation of cartilaginous tissue.

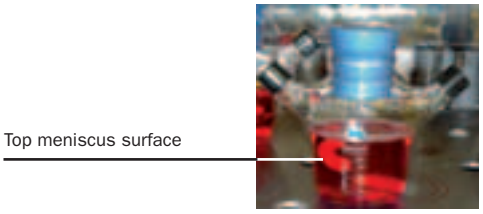


Peripheral tissue bonding between implant and capsule, tissue ingrowth and coverage of the surface. Collagen is stained blue.

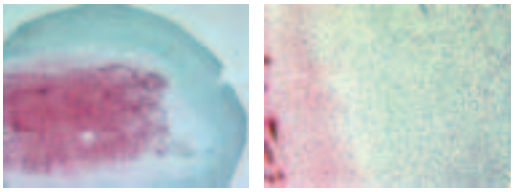
Tissue bonding between implant and residual meniscus. Collagen is stained blue.

3. Confirmation that a spinner flask or rotary cell culture system was the optimal bioreactor for creating meniscus-like constructs.

4. Implantation of a meniscus replacement device in a sheep model, indicating that correct sizing was important.



Meniscus prototypes in mixed flasks.



Safranin-O staining pictures of bovine articular chondrocytes cultured in mixed flasks for four weeks in disk shaped HA-based scaffolds.

G5RD-CT-2002-00703 – MENISCUS-REGENERATION
Innovative materials and technologies for a bio-engineered meniscus.

Total cost
€5 764 981
EC contribution: €3 689 213

Project duration
July 2002 – June 2007 (60 months)

Coordinator
Enrico Tognana – Fidia Advanced Biopolymers srl, Abano Terme, Italy

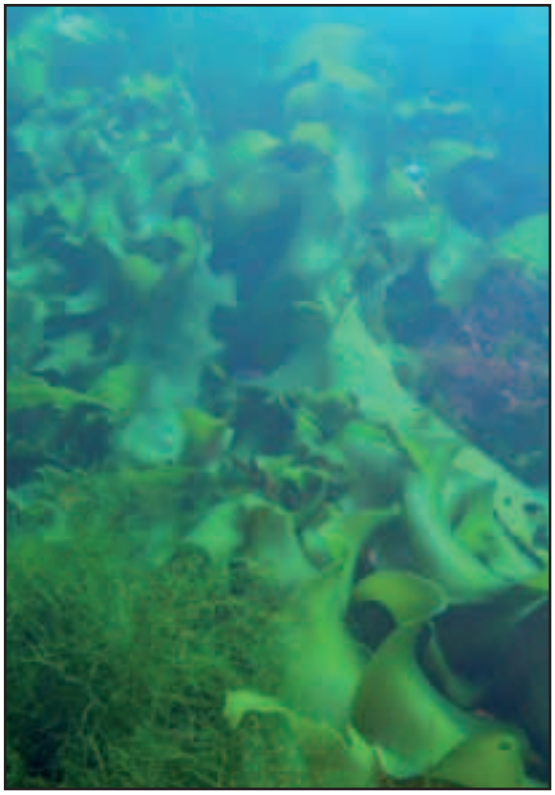
Marine algae hold key to better medical adhesives (2001-2005)

The tenacity with which marine algae cling to ships' hulls and underwater constructions suggests a remarkable adhesive capability. Responsible for fouling growths that reduce efficiency and cause costly damage, they are highly resistant to mechanical removal and all but the most environmentally unacceptable chemical preventive agents. The responsible bioadhesives have extraordinarily high cohesive strength and binding strength to the solid surfaces, enabling the organisms to remain attached under tensional conditions that are, in fact, comparable to those found in a surgical environment. To the consortium of the AB project, these qualities indicated a promising avenue of research in the hunt for more effective tissue adhesives for medical use, to replace painful traditional wound closure methods.

The partners undertook the purification, characterisation, gene expression and process elucidation of various algal bioadhesives. They then went on to isolate and characterise a particular candidate, which was tested and confirmed to be safe and efficient for use on human tissues.

Project successes

1. Isolation and characterisation of the proteins responsible FOR algal bioadhesion, followed by safety and efficiency testing for human tissue applications.
2. Implementation of a novel technique for electrophoretic separation of secreted adhesive proteins of *Enteromorpha* spores, avoiding conventional biochemical extraction, cross-linking and insolubilisation.
3. Proposal of a quartz crystal microbalance with dissipation (QCM-D) for the evaluation of adhesive bond formation and cross-linking of algal adhesives.
4. Demonstration that the *Enteromorpha* adhesive is inhibited in its cross-linking behaviour by thiol-reducing or thiol-capping agents.
5. Development of a mucoadhesion evaluation method for both dry compounds and gels.



G5RD-CT-2001-00542 – AB
Algal bioadhesives.

Total cost
€2 389 345
EC contribution: €1 774 777

Project duration
September 2001 – February 2005 (42 months)

Coordinator
Michael Friedlander – Israel Oceanographic & Limnological Research Institute, Department of Marine Biology and Biotechnology National Institute of Oceanography, Haifa, Israel

Biomaterials in FP6

Distribution of projects funded by EU in biomaterials (FP6)

Instrument	Number of projects	EC funding
STREP	28	€55.7 million
IP	6	€43.6 million
NoE	1	€7.3 million
SSA	1	€0.45 million
TOTAL	36	€107.1 million

FP6 differs from FP5 in that its main instruments, Integrated projects (IP) and Networks of Excellence (NoE), are larger in scale and involve greater numbers of partners in their consortia. Their goals are also more ambitious: targeting breakthrough innovations, rather than incremental advances on existing materials, processes and technologies. This Framework Programme also makes provision for the retention of existing instruments from FP5, such as Specific Targeted Research Projects (STREP) and specific Support Actions – as well as for initiatives designed particularly for SMEs.

Topics granted in the Sixth Framework Programme :

- Use of cells as micro-factories to produce and assemble molecular components for scaffold manufacturing.
- New intelligent biomaterials for cardiovascular tissue repair.
- New bioactive polymeric membranes and scaffolds for the reconstruction of liver tissue.
- Development of a bioartificial pancreas for type I diabetes therapy.
- Electrically functionalised hydroxyapatite to facilitate interactions with cells.
- Novel 3D scaffold structure for vascularisation of tissue-engineered constructs.
- Calcium phosphate cements for bone repair and regeneration.
- Chain integration for enhanced fully customisable medical implants.
- Load-bearing non-metallic biomimetic bone implants based on fibre-reinforced composites.

At the time of publication, all FP6 projects are ongoing. The achievements described for the illustrative examples on the following pages therefore represent only the progress to date. Further positive outcomes can be expected as the initiatives advance towards their conclusion.

Furthermore, the intention is that projects such as NoE should continue to develop beyond the end of their funded terms, as self-financing entities that will generate a cohesive long-term body of European research.

Towards a European virtual centre for tissue engineering (2004-2009)

The purpose of the Network of Excellence EXPERTISSUES is to establish a sustainable Virtual European Centre of Excellence in Tissue Engineering of Bone and Cartilage, linking top EU academic institutes with complementary industrial partners. By structuring and conducting research on a scale that will be competitive in the international arena, it will overcome the current fragmentation of European efforts in this field.

The programme comprises nine work packages:

- raw materials synthesis and development;
- scaffold design and processing;
- surface modification and tailoring of surface properties;
- production and characterisation of growth factors;
- controlled release strategies for tissue engineering and regeneration;
- cell isolation and culture methodologies;
- bioreactors and dynamic culturing of cells; and,
- in-vivo functionality assessment.

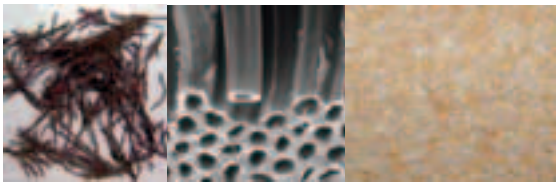
Coordination actions will include:

- joint planning of research activities and adjustment to meet individual groups' needs, while avoiding overlaps and duplication of effort;
- promotion of the mobility of personnel and sharing of know-how;
- creation of European post-graduate courses and training schemes;
- training for all partners in the state of the art of individual scientific fields, in order to create a common awareness of all the research areas;
- organisation of workshops and courses on specific subjects, both to discuss ongoing work and future directions for the network, and to create interfaces between the various scientific fields;
- creation of a shared electronic network for on-line exchange of information and results;
- launching a new TE journal and the publication of scientific books to educate future leaders in this highly interdisciplinary field;
- regular meetings (electronic and site visits) to discuss options and directions;
- optimisation of resource use, by building centralised databases of available equipment, raw materials, technologies and competences, etc.

Strong management will ensure the smooth running of the joint programme. Network activities are organised through a Joint Programme of Activities structured on three levels: Joint Programme of Integration, Joint Programme of Research, and Joint Programme of Dissemination.

An International Advisory Board has been created, comprising academic partners from leading institutions in USA, Canada and Singapore.

Algae



Exploitation of new materials of natural origin.

Polymer synthesis/molecular design.

Network of Excellence

NMP3-CT-2004-500283-2 – EXPERTISSUES
Novel therapeutic strategies for tissue engineering of bone and cartilage using second generation biomimetic scaffolds.

EC contribution
€ 7 300 000

Project duration
October 2004 – September 2009 (60 months)

Coordinator
Rui Reis – University of Mihno, Braga, Portugal.

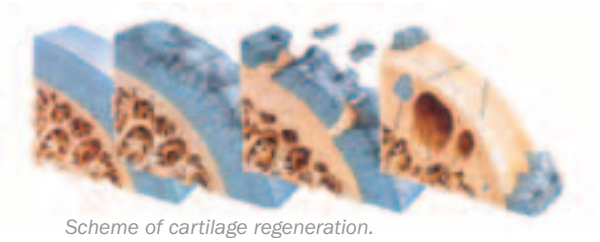
20 partners from 13 countries, including 9 of the EU Member States.

Taking tissue engineering further ahead (2005-2009)

Tissue engineering (TE) is a rapidly emerging collection of technologies aimed at the regeneration of tissues and organs for the treatment of disease and injury. It involves the seeding of porous, biodegradable scaffolds with donor cells; the culture of the resulting biohybrid construct in vitro, with or without the use of growth factors; and finally the implanting of the construct into the patient to induce and direct the growth of healthy new tissue.

The Integrated Project STEPS is studying four aspects of TE, two of which (skin and cartilage) are reasonably well advanced in terms of the science base and its introduction into clinical practice, one (bone) which is in the early stages of clinical development, and a fourth (visceral tissues), for which clinical adoption is still some years away.

Specific technological components include cell sourcing and manipulation, novel biomaterial development, bioreactor design and the integration of TE constructs into the living host. The programme also takes account of the socio-economic issues related to ethics and health economics. It will include an assessment of the public acceptability of these emerging technologies, and the ability of private and public health insurance to pay for them without detracting from more traditional medical procedures.



Scheme of cartilage regeneration.

Project goals/achievements

1. In-vitro production of artificial **skin** grafts to permit direct comparison of the long-term performance of TE treatments with that of traditional treatments for diabetic foot ulcers.
2. Determination of whether a TE product developed to treat traumatic focal **cartilage** defects could be exploited for the treatment of a chronic disease such as osteoarthritis. The team hopes to provide breakthrough scalable bioreactor-based technology for the manufacture of TE products on a large scale, while reducing production costs. It will complete the work by performing pilot studies with a limited number of patients to assess feasibility and safety.
3. Systematic coordination of human **bone** TE process variables, to a point where a satisfactory clinical outcome is attained. The 2D and 3D scaffolds being developed are based on esters of hyaluronic acid, poly-ε-caprolactone, poly-lactide, calcium phosphate and related composites. Advanced preparation methodologies have been employed in order to optimise porosity, transport, mechanical and degradation properties; and novel approaches to scaffold characterisation are being used to assess performance. Work is underway to design suitable bioreactors.
4. Focus on **visceral** TE indications in urology – i.e. bladder replacement or enlargement, and urethral stenosis, which require treatment by urethroplasty. Preliminary in-vivo studies have already shown promising results.

Integrated project (IP)

NMP3-CT-2004-500465 – STEPS
A system approach to tissue engineering processes and products.

EC contribution
€13 063 054

Project duration
March 2005 – September 2009 (48 months)

Coordinator
Alessandra Pavesio – Fidia Advanced Polymers s.r.l., Abano Terme, Italy.

The consortium comprises 23 partners from 13 European countries. It includes six industrial organisations, four of which are SMEs, and 17 academic centres.

Technologies for third generation biomaterials (2005-2008)

The STREP 3G-SCAFF is not only developing methods for the preparation of functional biomaterials for animal- or human-derived tissues, but also exploring the possibility of engineering both materials and cells to prepare the 'third generation' of designed biomaterials. These include a bioresorbable intelligent polymer/extra-cellular matrix (ECM) composite with a bioactive structure able to activate specific cells.

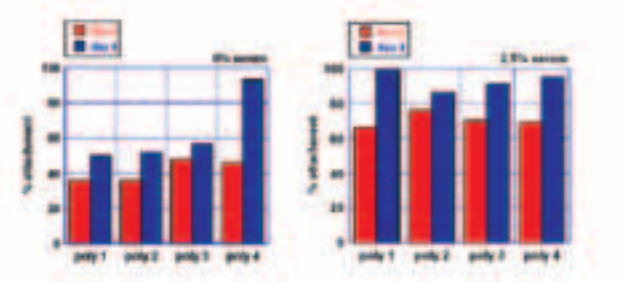
Development of bioactive material systems that are sensitive to enzymatic degradation of the populating tissue is also underway. The ECM components of the scaffold can be used directly by the populating cells as building blocks to remodel new tissue.

The cell/ECM-cell construct will be conditioned in a bioreactor to regulate the amount and orientation of the protein structure, followed by cell extraction from the scaffold prior to implanting in animal and human models.

Overall project plan of fabrication in 3G-SCAFF project.

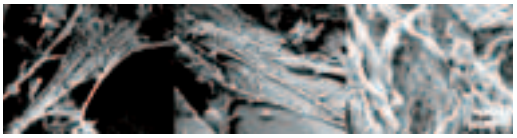
Project achievements

1. Preparation of a polymer compliant cell carrier. Poly(L-lactide-co-ε-caprolactone), poly(L-lactide-co-glycolide) and poly(ε-caprolactone) diol were synthesised, and scaled up from 10 g to kg scale. The polymers were melt processed to fibres/filaments and spun into yarn, which will be knitted into fabrics and used as cell carriers in the bioreactor.
2. Engineering of 'cell factories' for both human and murine fibroblasts, and Chinese hamster ovarian (CHO) cells. Use of cells expressing green fluorescent protein (GFP) has simplified the assessment of cell growth on polymers. Cell attachment was increased through the addition of serum into the culture medium, and cells were shown to proliferate well in the polymers tested.
3. Experimental production of ECM on polymers by culturing cells under dynamic conditions in a bioreactor demonstrated that cells attach well to polymer fibres and produced ECM proteins. The matrix produced in-vitro can be compared to acellular dermis, an ECM-based biomaterial in use today. Cells were distributed throughout the entire polymer construct and formed bridges between single fibres in the knitting.



Percentage of cells attached on weft knitted PLA-co-TCM polymer discs on day 2 and day 4. Cell attachment efficiency was compared in the absence (left) and in the presence of serum in the culture medium (right).

Spun yarn of poly (L-lactide-co-ε-caprolactone)



ECM deposited by fibroblasts cultured under dynamic conditions in a bioreactor. The left picture shows extracellular matrix fibres spanning between pores in the polymer carrier. The centre picture shows cells and matrix interacting tightly with the polymer fibres. As a reference material, the right picture shows acellular dermis.

STREP project

NMP3-CT-2005-013602 – 3G-SCAFF
Third generation scaffolds for tissue engineering and regenerative medicine.

Total cost
€1 801 248
EC contribution: €1 699 998

Project duration
March 2005 – February 2008 (36 months)

Coordinator
Jöns Hilborn – Uppsala University, Department of Materials Chemistry, Polymer Chemistry, Uppsala, Sweden

Artificial bone grafts mimic patients' own tissue (2004-2007)

Bone is the most frequently transplanted tissue, and autografts using bone sections taken from other parts of a patient's own body account for the majority of such procedures. However, autografts typically require secondary surgery, adding high costs to health services and increasing patient morbidity. Moreover, the availability of graftable material is limited in quantity.

Allograft bone provided by a compatible donor has been used as an alternative, but it shows low capacity for bone growth and resorbs more rapidly than autologous tissue.

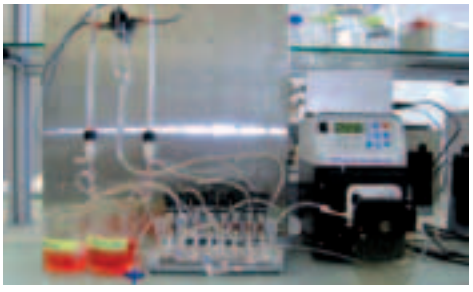
Consequently, there is global interest (and considerable market potential) in methods of rebuilding and restoring function to degenerated tissue by means of artificial implants. The high demand, coupled with recent progress in biomedical and biomaterial science, has stimulated the rapid expansion of bone tissue engineering. But a number of problems remain in transferring this approach from academia to a routine clinical environment.

The intention within AUTOBONE is to:

- produce a bioreactor capable of combining a tailored 3D porous matrix with stem cells from harvested bone marrow, delivering autologous hybrid bone graft materials with biological properties approaching those of true autologous bone;
- design and produce novel biomaterials and 3D scaffold architectures suitable for bioreactor use and bone tissue engineering;
- validate the autologous hybrid bone graft in preclinical animal studies.

Project achievements

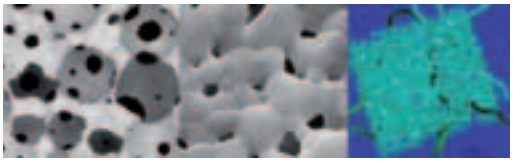
1. Completion of prototype reactor design, with configuration of a suitable scaffold chamber, integration of oxygen and pH sensors, and set-up of fluid-dynamic models.



Full set of automation hardware with prototype flow path.

2. Development of a scaffold suitable for use in the bioreactor, including identification and synthesis of the most appropriate hydroxyapatite (HA)-based materials.
3. Biomimetic synthesis to yield new bone-like composites made of HA nanocrystals and self-assembling type I collagen fibres, which showed a complete analogy with calcified natural tissues.
4. The bioreactor-based method to generate osteoinductive grafts was established using cells derived from human marrow aspirates. Cell phenotype, cell proliferation, and colony-forming efficiency were assessed following in-vitro culture, and the amount of bone formation monitored following in-vivo implantation.
5. In-vivo tests defined the model for medium/large-sized animal assessment.

Three-dimensional reconstruction of substitute from micro-CT images.



Bone formation in HA-Collagen scaffold.

STREP project

NMP3-CT-2003-505711 – AUTOBONE
Production unit for the decentralised engineering of autologous cell-based osteoinductive bone substitutes.

Total cost
€4 818 442
EC contribution: €2 296 892

Project duration
January 2004 – December 2007 (48 months)

Coordinator
Anna Tampieri – Consiglio Nazionale delle Ricerche – Istituto di Scienza e Tecnologia dei Materiali Ceramici/Dipartimento per la Bioceramica, Roma, Italy

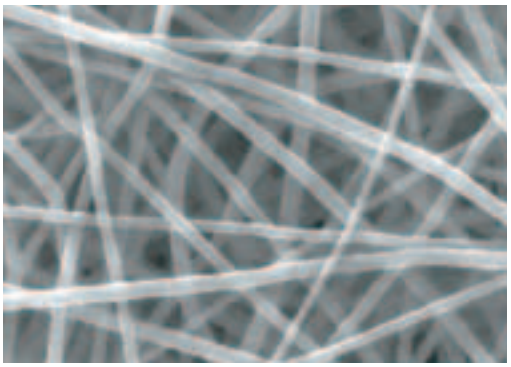
Engineered vascular grafts promise affordable heart repair (2005-2007)

Cardiovascular diseases are the most frequent cause of mortality in Europe. With an ageing population, the cost of current treatments could soon become unsustainable. New strategies have to be found. Tissue engineering, using a patient's own cells to replace the defective tissue, offers an ideal answer.

BIOSYS will develop new intelligent biomaterial systems with controllable bioresorbable and bioactive surfaces, able to activate specific cells and genes involved in tissue repair. Thus, the objective is to develop textile scaffolds for artificial vascular graft and artificial heart valves, and to test them both in-vivo and in-vitro.

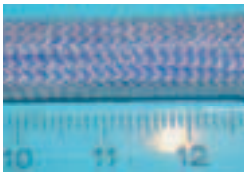
Project achievements

1. Fibre production and optimisation. Wet-spun, electro-spun and melt-spun polylactide (PLA) fibres were prepared. At a laboratory scale, fibre thicknesses down to some 40 µm were achieved, although the target is to reach around 20 µm.



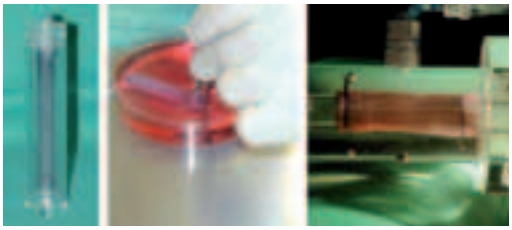
Electro-spun fibres. A uniform and dense fibre network developed using an adjusted injection rate; SEM micrograph, magnification 3500 x.

2. In-vitro cytotoxicity testing. Very good results were found for fibres spun from lower molecular weight polylactide, with no change in mechanical properties in-vitro within 25 weeks.
3. Manufacture of nanofibre structures by electro-spinning. Small interconnected pores initiate cell in-growth and provide a large surface area that can be utilised in controlled drug release.
4. Textile structuring. Three textile scaffold prototypes were manufactured. One has a warp-knitted structure for the vascular graft scaffold, while two different nonwoven types were made for the heart valve scaffold. Melt-spun fibres proved to be the most suitable for the vascular scaffolds, and wet-spun fibres for the heart-valve version.



Warp knitted vascular graft scaffold.

5. Cytotoxicity testing of fibres and meshes. The melt spun fibres showed no cytotoxic response on either of two cell lines tested.
6. Development of a heart valve implant. The first nonwoven version was seeded with standard human vascular-derived cells and cultured for up to six days. Analysis of the constructs revealed cell-to-polymer surface attachment and some in-growth into the polymer.
7. Development of the composite vascular graft, consisting of a porous textile structure (pore size 1-2 mm) and fibrin gel as cell carrier. The aim is to change from the currently used non-biodegradable mesh to a biodegradable textile poly-lactic acid (PLLA) structure. The co-scaffold model of PLLA and fibrin gel forms an intelligent multiphase drug release system.



Composite vascular graft: textile structure as scaffold, moulded with fibrin gel matrix.

STREP project

NMP3-CT-2005-013633 – BIOSYS
Intelligent biomaterial systems for cardiovascular tissue repair.

Total cost
€ 4 450 000
EC contribution: € 1 999 700

Project duration
January 2005 – December 2007 (36 months)

Coordinator
Michael Kloppels – 3T Textil Technologie Transfer Gmbh, Aachen, Germany

Artificial pancreas could end insulin injections for diabetics (2004-2006)

Four to five million people in Europe and about 80 million worldwide suffer from type 1 diabetes, characterised by deficient insulin secretion and resulting in hyperglycaemia (an elevated concentration of glucose in the blood). This doubles the risk of death from coronary diseases, and can lead to acquired blindness or chronic renal failure.

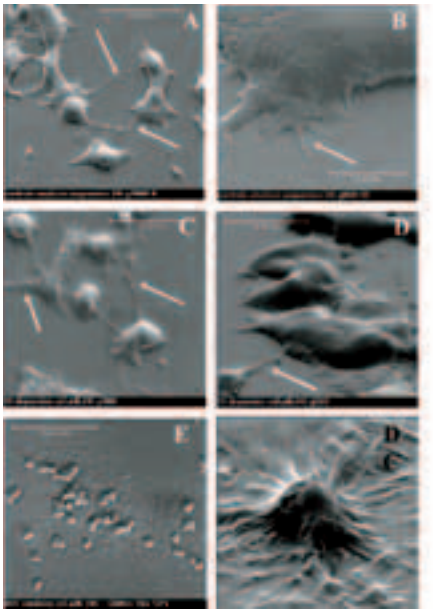
Apart from transplantation of the pancreas or of pancreatic tissue 'islets', the only form of therapy for diabetes type 1 is to administer insulin by daily multi-injections or implantable pumps.

Several research groups have developed methods to gather large numbers of pancreas islets from pigs. Unfortunately, transplantation of these into humans would induce a severe immune rejection, which can probably only be avoided by encapsulating them within protective semi-permeable membranes. Various encapsulation methods have been explored in the past, but with only limited success. Now, the BARP+ project is studying a new system that shows great potential.

The goal is to develop a prototype bioartificial pancreas suitable for encapsulation of insulin-secreting tissue and small enough for implantation into the human body. The device must provide selective permeability to insulin and glucose, while excluding other molecules responsible for rejection or unwanted toxic effects.

Project achievements

1. Development of the prototype. Islets of animal origin were enclosed in a device formed by a support and a polycarbonate membrane, with an extra cellular matrix in the encapsulation chamber to prevent aggregation of the islets. By association of 20 devices in a plate-type support, it was possible to implant up to 20 000 pancreatic islets, as necessary for testing on a mini-pig. Sterile macrodevices were implanted into normal mini-pigs and their biocompatibility studied after up to 92 days of implantation. Despite the induction of fibrosis, there was no observable inflammatory response, nor any significant effect on the peripheral immune system.
2. A method for the preparation of human pancreatic islets led to clearance of contaminants in 94% of cases, thus demonstrating the feasibility to provide islets for seeding. Ethylene oxide (EtO) was used to sterilize the membranes and the various parts of the device.
3. Evaluation of alternative insulin-secreting cells. Novel insulin-secreting cells were generated and two selected. It proved easily possible to accommodate up to several hundreds of pseudoislets in the device.
4. Survival of the graft. Studies demonstrated that collagen had no effect on the viability and functionality of islets. Fluorocarbons were shown to have a beneficial effect on tissue preservation and, by preventing cell adhesion, to improve cell viability.



MIN-6 cells by scanning electron microscopy in control (A (G 1000) & B (G 9000)), in presence of phospholipids dispersion (C (G 1000) & D (G2500)) and in presence of fluorocarbons emulsion (E (G500) & F (G5000)).

STREP project

NMP3-CT-2003-505614- BARP+
Development of a Bioartificial Pancreas for Type I Diabetes Therapy.

Total cost
€3 622 479
EC contribution: €2 495 600

Project duration
January 2004 – December 2006 (36 months)

Coordinator
Alain Belcourt – Centre Européen d'Etudes du Diabète – CeeD. Strasbourg, France.

Liver cell constructs point the way to organ regrowth (2005-2008)

The development of new intelligent materials able to activate specific responses in human liver cells could provide an inexpensive means of studying hepatic diseases and infections – and eventually point the way to regeneration of the liver itself.

LIVEBIOMAT targets the design and development of new bioactive polymeric membranes and scaffolds for the reconstruction of a liver tissue model in-vitro. Isolated liver cells rapidly lose their specific functions when maintained under standard in-vitro cell culture conditions, so a fresh approach is crucial to the investigation of hepatocyte activity in a controlled environment. Engineered liver tissue constructs would form valuable tools for pre-clinical drug testing and toxicology studies, leading to improved technologies for the production of pharmaceuticals and vaccines.

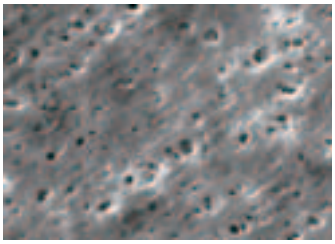
More ambitiously, the partners also aim to develop biodegradable polymers for in-vivo reconstruction of liver tissue, which will represent an important advance in the prevention, diagnosis and treatment of problem diseases.

Project achievements

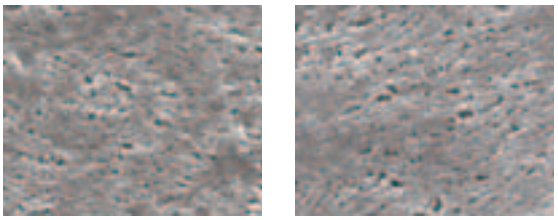
1. Bioreactor construction. A scalable hepatic mini-bioreactor model has been built, capable of high throughputs for in-vitro pharmacological screenings. This system is being used in primary rat hepatocytes.
2. Membrane trials. Semi-permeable polymeric membranes were prepared from a blend of modified polyetheretherketone (PEEK-WC) and polyurethane (PU), with regularly distributed 0.1 µm surface pores. Hepatocytes cultured on this surface exhibited higher metabolic rates than those cultured on a collagen control. The polymer is compatible with human hepatocytes, and is thus applicable as a substrate for in-vitro reconstruction of human liver tissue.

The mini bioreactor as a system for pharmacological in vitro screenings.

3. Surface modification. In order to optimise the membranes for biomolecule immobilisation, cell adhesion and expression of the hepatocytes' metabolic functions, various plasma modification processes were applied. The modified surfaces were used as substrates to promote the self-assembly of a peptide coating (pdAA), without significant pore size alteration or structural change.



SEM image of the PEEK-WC-PU membrane surface.



SEM images of the PEEK-WC-PU membrane (left micrograph) and the PEEK-WC-PU membrane after plasma deposition of acrylic acid (right micrograph).

STREP project

NMP3-CT-2005-013653 – LIVEBIOMAT
Development of new polymeric biomaterials for in vitro and in vivo liver reconstruction.

Total cost
€3 329 896
EC contribution: €2 299 906

Project duration
April 2005 – March 2008 (36 months)

Coordinator
Augustinus Bader – University of Leipzig, Biomedizinisches-Biotechnologisches Zentrum, Leipzig, Germany

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