Original article

□ Materials and technologies for craniofacial tissue repair and regeneration

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SUMMARY: *The term "cranioplasty" refers to the correction of bone defects or deformities in the cranium using a biocompatible material. Over the past years, a wide range of materials has been employed to repair cranial defects. Titanium, especially in the form of sheet and mesh devices, poly-methyl-methacrylate based bone cement and hydroxyapatite have been already used for cranioplasty. Such materials present different physico-chemical properties and biological performances. Moreover, the above mentioned materials may be employed alone or in combination with other materials such as calvarial bone. In particular, autologous bone and bone cement represent the two most common approaches to create a repair. However, the advanced design of structural craniofacial devices needs materials with complex combinations of properties. The present chapter will deal with concepts in implant designing, materials and engineering technologies for cranioplasty, as well as future trends in the field. Synthetic non-degradable, partially degradable and fully degradable biomaterials, spanning from acrylic cements to materials for manufacturing prostheses and scaffolds for hard tissue regeneration, will be focused. Criteria and clinical indications for cranioplasty will be briefly introduced. Then, materials for repair as well as manufacturing techniques will be described taking into consideration their basic features, advantages and disadvantages. A particular emphasis will be given to rapid prototyping technologies, custom-made polymer-based composite prostheses and scaffolds. Accordingly, the possibility to integrate different techniques such as 3D image capture, 3D modelling and rapid prototyping, with those related to the materials preparation, will be highlighted in order to design custom-made prostheses or scaffolds with a 3D complex geometry.*

KEY WORDS: *Craniofacial tissues, Cranioplasty, Materials, Prosthesis, Technologies, Tissue engineering, Scaffold.*

□ Materiali e tecnologie per la riparazione e rigenerazione dei tessuti cranio-facciali

RIASSUNTO: *Il termine "cranioplastica" si riferisce alla correzione di difetti o malformazioni presenti nel cranio tramite l'uso di un materiale biocompatibile. Nel corso degli anni un ampio range di materiali è stato impiegato per la riparazione di difetti cranici. Titanio, specialmente sotto forma di lamine e reti, cemento osseo a base di polimetilmetacrilato e idrossiapatite sono stati ampiamente utilizzati. Tali materiali presentano differenti proprietà chimico-fisiche e performance biologiche. Inoltre, essi possono essere impiegati da soli o in combinazione con altri materiali. In particolare, gli approcci generalmente adottati prevedono l'utilizzo di osso autologo e cemento osseo. Tuttavia, la progettazione avanzata di strutture cranio-facciali richiede materiali caratterizzati da una complessa combinazione di proprietà. Il presente capitolo tratterà concetti nell'am-*

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Topics in Medicine 2010; Special Issue 1-4.
ISSN: 1127-6339. *Fascicolo monografico: ISBN: 978-88-8041-028-7.*
"Cranial demolition and reconstruction. Cranioplasty in one step", editors B. Zanotti, A. Verlicchi and P.C. Parodi
 www.topicsmedicine.com

bito della progettazione di protesi, materiali e tecnologie ingegneristiche per la cranioplastica, delineando gli sviluppi futuri in tale settore. Saranno oggetto di analisi i biomateriali sintetici non-degradabili, parzialmente degradabili, totalmente degradabili, che vanno, quindi, dai cementi acrilici a quelli per la realizzazione di protesi e scaffold per la rigenerazione di tessuti duri mineralizzati. Verranno brevemente introdotti criteri e indicazioni cliniche circa la cranioplastica. Successivamente, i materiali utilizzati per la riparazione di difetti cranici e le tecnologie di fabbricazione verranno descritte prendendo in considerazione aspetti di base, vantaggi e svantaggi. Particolare enfasi sarà data alle tecniche di prototipazione rapida, a protesi e scaffold custom-made in materiale composito a matrice polimerica. A tale proposito, verrà illustrata la possibilità di integrare differenti tecniche come quelle di acquisizione e analisi delle immagini e di prototipazione rapida con quelle relative alla preparazione dei materiali da utilizzare, al fine di ottenere protesi o scaffold custom-made caratterizzati da una complessa geometria tridimensionale.

PAROLE CHIAVE: *Tessuti cranio-facciali, Cranioplastica, Materiali, Protesi, Tecnologie, Ingegneria dei tessuti, Scaffold.*

□ INTRODUCTION

The term "cranioplasty" refers to the correction of bone defects or deformities in the cranium through the use of a biocompatible material. As reported in the literature, several materials have been employed to fill holes in the skull, which arose from injury, disease or operations. Precious metals, such as gold and silver, as well as autologous bone graft, that means the patient's own bone, and, more recently, Poly-Methyl-Methacrylate (PMMA)[84], have been used to fill defects.

It is well documented that skull remnants from ancient graveyards in Peru evidenced signs of trephination (i.e., the creation of a hole in the skull) and repair.

Currently, the two most common approaches to create a repair are autologous bone[92] and acrylic resin, in the form of PMMA, that is commonly known as bone cement[12,74,77].

However, in this field, further materials have also been employed achieving different degrees of success. For example, thin titanium sheet can be suitably curved and formed under pressure in order to properly fit the contour of the skull. Joffe et al. (1999)[48] described the use of computerized three Dimensional (3D) imaging and automated milling of models to obtain accurate titanium plates for the reconstruction of craniofacial defects. These plates were fitted by using lugs, and fixation screws were used to attach them to the outer surface of the skull.

To repair small holes in the skull, HydroxyApatite (HA)-based cement alone or used with titanium mesh has also been used[4]. This hydroxyapatite cement reconstruction was also approved by the Food and Drug Administration for the repair of cerebrospinal fluid leaks in 1996.

Brandt and Haug (2002)[8] proposed a technique through which a titanium mesh has been moulded into shape on polyurethane skull replica, providing a more precise adaptation and reproducing the anatomic form, especially in the case of large voids. Schipper et al. (2004)[88] also reported a comparison between titanium-dynamic mesh and prefabricated titanium implants in surgical reconstruction procedures of the skull base, in terms of indications, limitations and costs. As result, titanium mesh was selected as the implant of choice for bone defects with a surface area that is smaller than 100 cm^2.

Accordingly, the present chapter will deal with concepts in implant designing, materials and engineering technologies for cranioplasty, as well as future trends in the field.

□ CRITERIA AND CLINICAL INDICATIONS FOR CRANIOPLASTY

Artico et al. (2003)[5] evidenced that both decompressive surgery and re-implanted bone may cause infections after a neurosurgical procedure. This damages the patient's own bone or makes it out of use, thus considering the possibility to replace it with a suitable biomaterial.

As already stated, unlike an autologous implant, that is directly derived from the same patient, an alloplast implant is manufactured by using an inert biocompatible material.

In literature, an interesting work by Rotaru et al. (2006)[81] highlights that the repair of cranial defects surely provides protection to the brain and good aesthetic results for the patient, also leading to possible alleviations of several neurological symptoms (i.e., depression, headache, etc.). Furthermore, it seems

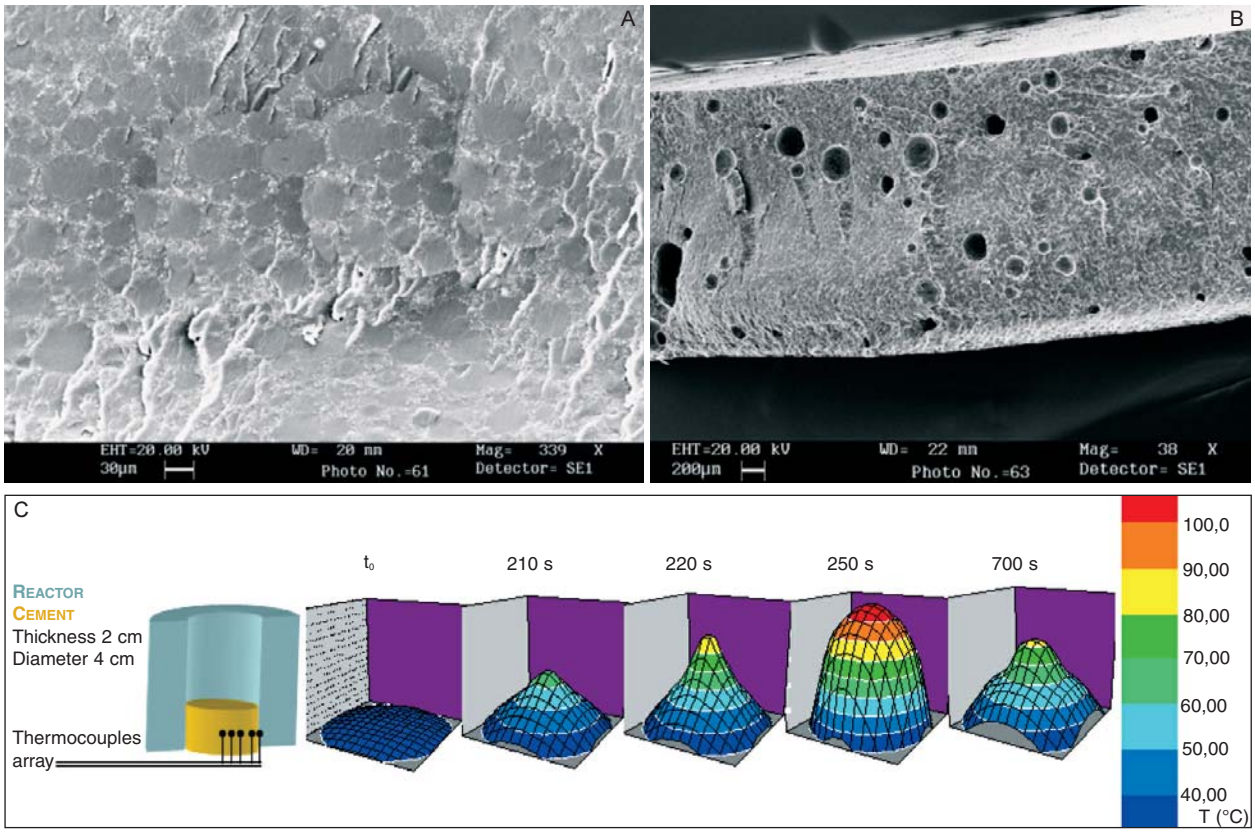

Figure 1. A. Scanning Electron Microscopy (SEM) of a Poly-Methyl-Methacrylate (PMMA) cement showing the presence of a pre-polymerised phase dispersed in a PMMA matrix. B. SEM image of a PMMA cement showing voids in the bulk of the material. C. Temperature profiles developing during the setting reaction of a traditional PMMA cement.

that a neurocognitive function will be also recovered by the patient, as evidenced by Agner et al. (2002)[3].

MATERIALS FOR REPAIR

As previously described, a wide range of materials could be employed to repair cranial defects.
In this context, titanium (in the form of sheet and mesh devices), acrylic resin and hydroxyapatite have been already used for cranioplasty[103]. These materials clearly present different physico-chemical properties and biological performances. However, titanium, acrylic resin and hydroxyapatite may be employed alone or in combination with other materials, bone dust or calvarial bone.
Usually, cranial implants are manufactured taking into account the shape and size of the defect, thus making a plaster impression through the overlying skin[36,103]. The first step is represented by the shaving of the patient's scalp. Then, the margins of the defect are precisely individuated, marked and, hence, transposed onto the plaster impression.
However, the defect contour will be altered by the eventual presence of oedema, haemorrhage, swelling and overlying muscle. Accordingly, implants obtained using this approach may result flat and often need further manipulations in order to properly match the defect[49,103].
With regard to the materials used in the clinical practice, acrylic resin is normally employed by the surgeons. Also known as bone cement, it is mainly used in the orthopaedic surgery for anchoring hip and knee prostheses to the bone[18]. In particular, the fixation of total knee components can be considered as the current "gold standard", and many studies have also reported excellent long-term results with cemented total arthroplasty[78,79].
PMMA-based cements are the most common biomaterials used to anchor a prosthetic component to the bone.
Basically, bone cement is provided to surgeons in the

form of a solid powder phase made of PMMA and/or copolymers and a liquid monomer component. The powder also contains diBenzoyl-Peroxide (BPO) as initiator for radical polymerization, a radio-opaque substance and sometimes an antibiotic (i.e., gentamicin), that may be released after the implantation. The main components of the liquid phase are Methyl-Methacrylate (MMA) and, in some bone cements, other esters of acrylic acid or methacrylic acid, one or more amines (i.e. activators/co-initiators for the formation of radicals), a stabilizer and, possibly, a colorant[19,54].

By mixing the powder polymer and liquid monomer component, an exothermic reaction is obtained. Accordingly, during this process, the temperature of the paste increases drastically and laboratory experimental activities have frequently shown that the paste may also reach temperature greater than 70 °C during the reaction[59,61,103]. These high temperatures may provide several drawbacks such as tissue damage and, hence, the loosening of the prosthetic implants. However, the temperatures reached during the polymerization process are strongly dependent upon the mass of the paste used. For this reason, it is worth noting that surgeons employ an amount of cement paste, which is smaller than that normally used in laboratory experiments. Moreover, necrosis observed during implantation may be mainly related to the surgical approach (i.e., drilling, reaming, etc.)[47,103].

During cranioplasty, the yet malleable and warm paste is placed onto the skull defect before the setting phase. A damp gauze over the dura is also used to function as heat protection. Thus, the skull defect is fitted by the paste that is formed by mixing manually. Then, the paste hardens making the desired hard barrier.

After the hardening phase, the resin-based barrier is held in position using titanium mini-plates that are fixed to the polymeric reconstruction and the skull with screws.

It appears clear that during a surgical intervention the presence of an exothermic reaction and, consequently, of a heated material close to the surface of the brain or dura may create many perplexities. The use of a pre-polymerised PMMA phase in the form of micro-spheres is a common approach adopted by manufacturers in order to limit temperature rise and shrinkage during the polymerisation process of an applied PMMA cement. The Scanning Electron Microscopy (SEM) image of a bone cement reported in Figure 1A clearly shows the micro-spheres phase dispersed in a PMMA matrix. However, a significant temperature rise is widely documented. Figure 1C shows temperature profiles developing in a Teflon reactor during the polymerization process of a commercial bone cement characterised by a 2:1 weight ratio between the solid and the liquid phases. Temperature peaks occurs in the bulk of the cement and these values may be as high as 100 °C.

In any case, as previously introduced, the use of a damp gauze with saline solution placed between the acrylic resin and dura tissue may protect from the polymerization heat.

However, another drawback in using the acrylic resin is related to the patient and medical staff exposure to the monomer, since in his work Meel (2004)[67] has reported one death attributed to a systemic allergic reaction as a consequence of MMA exposure. Moreover, the entrapment of air during the mixing phase of acrylic cements leads to the creation of voids, which are clearly shown in Figure 1C, that decrease mechanical properties and increase brittleness due to a stress rise effect.

Even though Blum et al. (1997)[7] have demonstrated that in paediatric patients acrylic resin for cranioplasty is not recommended, Moreira-Gonzalez et al. (2003)[68] have found that bone graft and PMMA may be considered the best materials for a long term outcome[103]. Many studies[50,103,105] underline the use of titanium sheet for cranioplasty, following a technique developed in the Northern Ireland during a period of civil strife, as reported by Gordon and Blair (1974)[35]. The plaster of Paris was used to make an impression of the skull defect, then creating a suitable template and, hence, a stone former. Successively, the titanium sheet was compressed onto the former. The titanium sheet was placed over the defect and anchored using screws with flat head[103].

Even though Hieu et al. (2002)[38] have reported interesting results in terms of low rejection rate for titanium, in a recent study Eufinger et al. (2005)[26] have demonstrated a lower success related to the use of titanium for cranioplasty. In particular, the main complications were found treating defects with a surface area greater than 100 cm^2.

As an alternative to PMMA-based bone cement in the field craniofacial reconstruction, in conjunction with titanium mesh Ducic (2002)[22] have proposed the use of hydroxyapatite, in the form of a powder mixed with water to obtain a paste.

Historically, in 1986, Brown and Chow[10,99] described a calcium phosphate cement that self-hardened and

formed pure HA. Since its introduction, HA has been considered for a wide range of osseous reconstructions, and seems to provide an enhancement in comparison with the other alloplast materials currently available for craniofacial reconstructions. As already known, it consists of natural minerals, osseointegrates, is self-curing and forms during an isothermic setting process[10,82,99].

Several authors have suggested the use of HA cements especially in the case of calvarial repair even with direct dural contact, frontal sinus obliteration, and other skull and skull base reconstructions[16,21,40, 99,110].

Previous studies have demonstrated that HA-based cements are safe for various craniofacial reconstructions[10,16,22,40,82,99].

Even though HA is biocompatible and osteoconductive, studies on HA cranioplasties[23] have evidenced drawbacks mainly due to delamination rate and bacterial contamination.

However, an interesting work by Verret et al. (2005)[99] investigated the long-term performance of different HA-based cements, specifically focusing the attention on the role of eventual radiation, implant location, and cement type, finally suggesting them as safe materials in craniofacial reconstructions.

□ MATERIALS SELECTION: PROPERTIES, ADVANTAGES AND DISADVANTAGES

Current materials for cranioplasty encompass autologous or homologous bone grafts, as well as metals, polymers and ceramics, either alone or in combination. It is difficult to find the ideal solution among all the synthetic or biological materials employed for human cranioplasty. Clearly, biocompatibility, radiolucency, short- and long-term mechanical strength, malleability, represent requirements that implants for cranioplasty have to satisfy.

Over the past two centuries, due to the absence of need to harvest donor bone and because of bone's tendency to scar or reabsorb, research attention has been focused on the use and development of alloplastic materials[32,52,60,76,107].

Moreover, many drawbacks are related to foreign implant material such as excessive inflammation, risk of infection, the impairment of cranial follow up imaging and of irradiation therapy[32,80,87,107].

Ceramic hydroxyapatite is the most biocompatible material because it may be incorporated into bone. However, as the other ceramic materials, it results brittle and tends to fracture, thus resulting impossible an eventual plate fixation. Although fully bioresorbable HA-based cements have preliminary highlighted interesting results[13,107], enhancements regarding to infection, mechanical strength, and comfort through good fitting are required, as well as further studies should be performed to evaluate the long-term performance[98,107].

PMMA-based resin is the most commonly used material for alloplastic cranioplasty. However, the brittleness of PMMA can cause the fracture of the plate. Using PMMA, further problems are related to the involved exothermic reaction, that responsible for significant local heat generation, and to the unreacted monomer.

Like ceramics and polymers, also metals and alloys (i.e., tantalum, cobalt alloy, vitallium, gold, stainless steel, aluminum) show several shortcomings. Such materials result difficult to shape, transmit heat and cold too readily, their radio-opacity creates problems in postoperative imaging. CT and conventional Magnetic Resonance Tomography (MRT) are unusable for metallic devices; however, only turbo-spinechosequences in MRI can be employed. In addition, ionization, corrosion and infection are considered further problems generally due to the use of metallic materials.

Among metallic materials, titanium seems to present better properties[11,107], even though deposition of titanium in lymph nodes has been observed[102,107]. Titanium is malleable and light in weight, while showing a high mechanical strength. Through MR investigation titanium does not heat up and generates no artefact on MRI analysis[11,107]. Conversely, it results opaque on X-rays[27,107] and generates several artefacts on CT analysis. Polymer-based composite materials represent an alternative choice to overcome drawbacks related to ceramic, polymeric and metallic materials[72].

For example, in orthopaedic surgery one of the most common problems is represented by the mismatch of stiffness between the bone and metallic or ceramic implants, that negatively affects the bone remodelling and healing process. Accordingly, the implanted devices should be biocompatible and characterized by appropriate mechanical properties. Polymer-based composite biomaterials have attracted much attention because of their tailorable properties that may match those of the host tissues. Table 1 reports the elastic moduli of human adult bone tissues from different

Material	Testing condition	Direction	Elastic Modulus (*GPa*)	Reference
Trabecular bone from the incisal region of the mandible	Compression	Parallel to the mandible arch	2.2	*O'Mahony et al., 2000*[73]
		Superior-inferior	0.12	
		Labial-lingual	1.1	
Trabecular bone from the premolar region of the mandible	Compression	Parallel to the mandible arch	0.99	
		Superior-inferior	0.05	
		Labial-lingual	0.09	
Trabecular bone from the condyle region	Compression	Superior-inferior	0.431	*Giesen et al., 2001*[31]
		Medio-lateral	0.127	
Cortical bone from the symphysis of the mandible	Ultrasound	Parallel to the mandible arch	21.1	*Schwartz-Dabney et al., 2003*[90]
		Perpendicular to the mandible arch	16.8	
Cortical bone from the mandible	Bending	Parallel to the mandible arch	17.5	*Hara et al., 1998*[37]
		30° from the mandible arch	14.3	
		60° from the mandible arch	11.7	
Cortical/trabecular bone from the skull	Compression	Tangential	5.58	*McElhaney et al., 1970*[56]
		Radial	2.41	
Cortical/trabecular bone from the macaca mulatta	Compression	Tangential	6.47	
PMMA (*Symplex-P*)	Bending	Isotropic	2.6	*De Santis et al., 2003*[19]
PMMA (*CMW1*/Gentamicin*)			2.3	
Ti6Al4V**	Ultrasound	Isotropic	100	*Fukuhara et al., 1993*[30]
Titanium alloys	Compression	Isotropic	110-117	*Staiger et al., 2006*[93]
CoCr Alloys			230	
Stainless steel			189-205	
Synthetic hydroxyapatite			73-117	
Glass fiber reinforced PEI	Tensile	Longitudinal	14.3	*De Santis et al., 2010*[18]
Carbon fiber reinforced PEI	Bending	Longitudinal	57.7	

Table 1. Elastic modulus of human adult bone tissues from different sites of the skull and synthetic biomaterials. *Legend*: *CMW1 is an acrylic bone cement; **Ti6Al4V is a titanium alloy that has been widely used for biomedical applications; CoCr = Cobalt Chrome (alloy); PEI = Poly-EtherImide.

sites of the skull and synthetic materials. Both trabecular and compact bones are highly anisotropic, that is properties depend on loading direction.

In the mandible it has been suggested that the anisotropy is affected by the teeth-mandible joint and adaptation due to chewing. Of course, PMMA and metal alloys are considered isotropic materials, therefore they are not capable to reproduce the typical anisotropy of bone. On the other hand, composite materials, such as fiber reinforced polymers, can be conveniently designed in order to match elastic properties of bone.

A "composite material" is the result of a combination, on a macroscopic scale, of two or more materials differing in terms of composition or morphology, in order to obtain specific physical, chemical and mechanical properties. The resulting composite material may possess a combination of the best properties of their constituents, and often other interesting properties which are not shown by the single constituents[33, 51,63,72,89].

Over the past years, composite materials with polymeric matrices, that are also defined as polymer-based composite materials, have emerged as suitable candidates for load bearing applications in several fields. The polymeric matrix and its interaction with a reinforcing phase, that can be in the form of continuous or discontinuous high stiffness fibers and particles, plays a crucial role in controlling the properties of a composite. Since fiber-reinforced polymers show

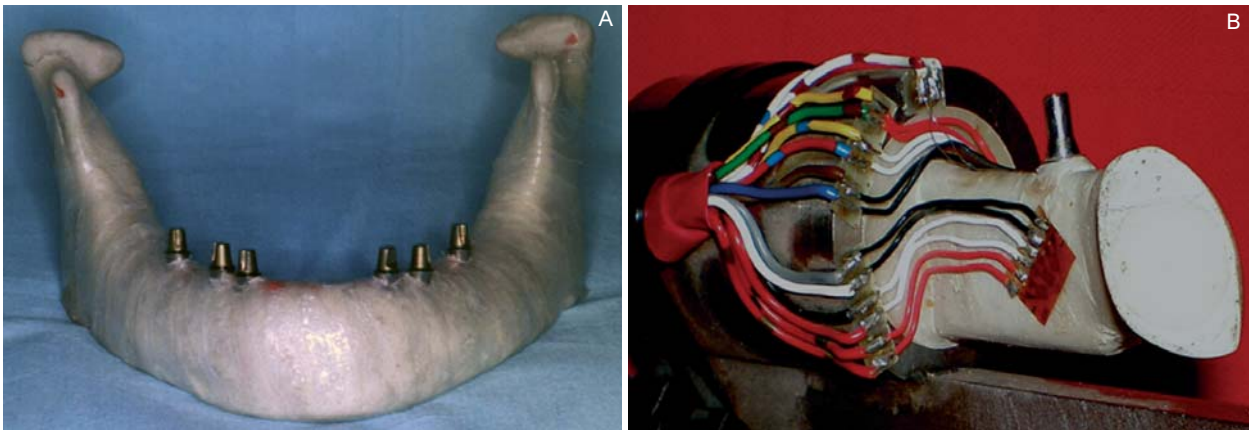

Figure 2. A. A composite model of human mandible characterised by a Fiber Reinforced Polymers (FRP) outer shell reproducing elastic properties of cortical bone by suitable orienting glass fibers. B. Cross section of the composite mandible showing the PMMA core and the FRP outer shell.

high strength and stiffness to weight ratios, they have gained research attention.

Accordingly, the attention was focused on a composite cranial implant consisting of an epoxy resin matrix reinforced with carbon fibers. These Carbon Fiber Reinforced Polymer (CFRP) implants have been clinically employed since the 1980s[43] in several medical fields[1,6,29,43,53,71,86,94-97,107].

An interesting feature of CFRP implants is that they may repeatedly be sterilized by autoclaving, thus allowing their reimplantation[107]. In addition, they are radiolucent and do not create problems during electroencephalographic and radiographic evaluation [29,107]. Moreover, the use of CFRP implants does not influence irradiation therapy[29,107]. Biocompatibility, innovative design, radiolucency, possibility to obtain specific and high mechanical performances, excellent functional and aesthetic results, is crucial factors that have attracted research attention. By using the FRP approach and the filament winding technology it has been possible to biomechanically reproduce the anisotropy of human connective tissues through synthetic biomaterials[17]. In particular, by using PMMA and glass fiber reinforced polymers it has been possible to replicate an edentulous human mandibles[20] reproducing the anisotropy of cortical bone (Table 1). Figure 2A shows a composite model of human mandible. Glass fibers were mainly oriented parallel to the mandible axis in the arch site, while they were mainly oriented at 45° in the ramus. These directions are suggested to be the main orientation of osteons into the cortical bone of the mandible. Figure 2B shows a cross section of the composite mandible, here a PMMA core, reproducing the elastic properties of trabecular bone (Table 1) and a 2 mm thick FRP, reproducing the anisotropy of the cortical bone are well evident.

□ MANUFACTURING TECHNIQUES

Alloplastic materials may be fabricated through *direct* or *indirect* techniques. In particular, direct techniques allow to manufacture alloplastic materials i*n situ* (i.e., on the surgical site), whilst indirect techniques are used to prefabricate them before implantation using several modeling techniques.

Clearly, large or complex defects, often located within the most visible parts of the skull, are difficult to restore for surgeons[107]. The fronto-temporobasal and the fronto-orbital region involving the supraciliary ridges seem to be a great challenge in this field[59,107]. To reconstruct cranial bone, the use of intraoperatively modeled prostheses strongly limits the material choice, often causing drawbacks related to the implant shape and size and its long-term performances. Furthermore, the use of alloplastic materials for intraoperative modelling may lead to an inflammatory tissue response, and conventionally prefabricated cranioplasty implants require complex approaches.

Through the impression of alginate-based materials it results possible to obtain a suitable mould of the patient's original bone flap[107,108]. Consequently, the accuracy of the indirect material implants is related to the accuracy of the defect model. However, the traditional fabrication methods of cranial implants involv-

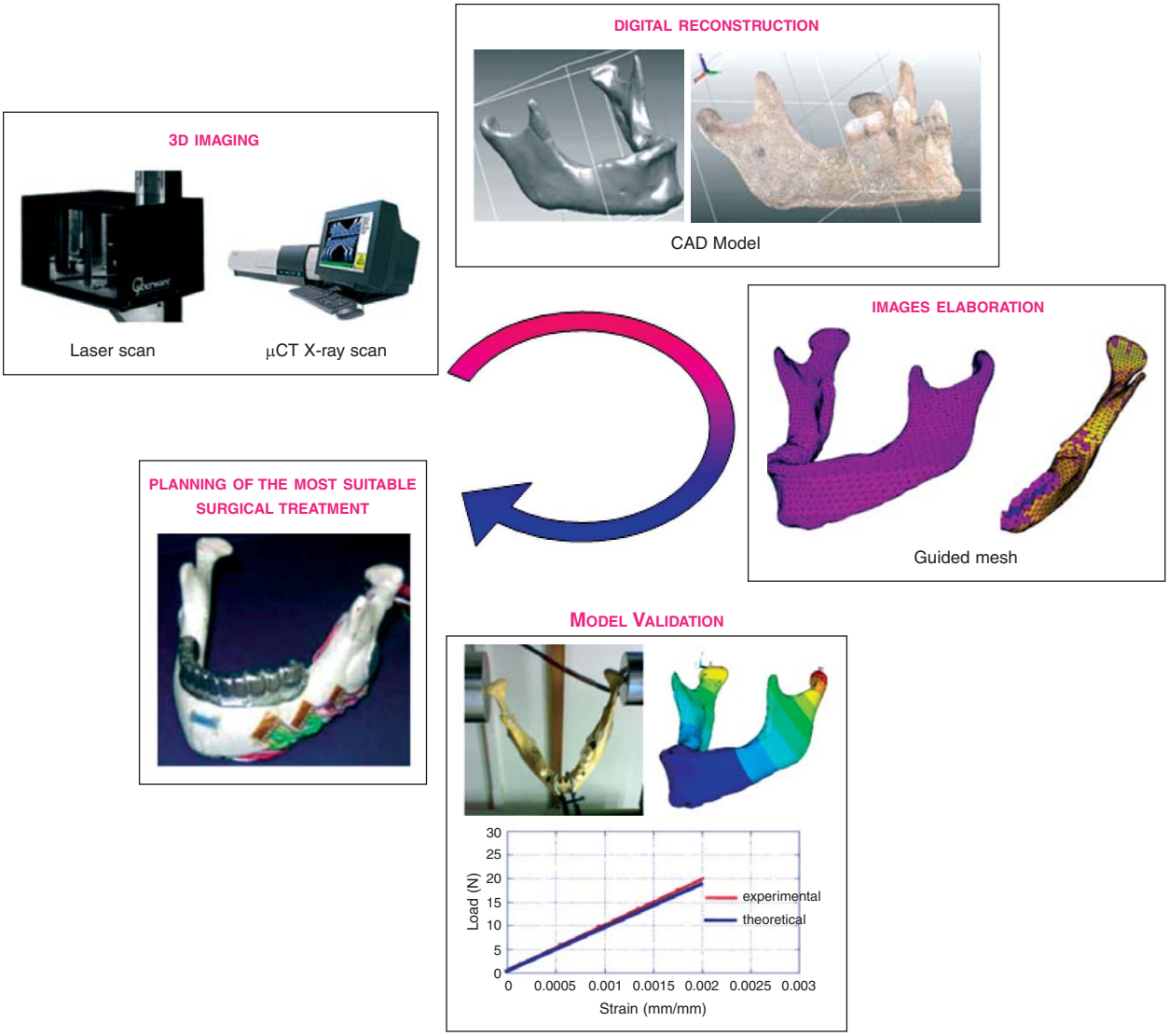

Figure 3. Typical sequence of computer assisted strategies in order to suitably plan the surgical treatment of an edentulous mandible.

ing scalp impressions by the surgeons may provide several dimensional and contour inaccuracies.

The introduction of Computer Aided Design and Manufacturing (CAD/CAM) techniques allows the prefabrication of custom-made medical implants[2,25,100]. Using these CAD/CAM systems, 3D models of the bone defect can be generated after acquisition, transfer, and evaluation of CT or MRI data. Then, the implant is designed and manufactured in a direct fashion by a numerically controlled milling machine[48,50,107] or, more recently, by StereoLithography (SL) and template modeling.

Figure 3 reports the typical sequence of computer assisted strategies in order to suitably plan the surgical treatment of an edentulous mandible. Non destructive 3D imaging through X-ray and MRI represent the main source of digital information that can be clinically available. Micro-CT and LASER scanners represent the main laboratory equipments to finely define the 3D geometry. DICOM (Digital Imaging and COmmunications in Medicine) files, tif images of slices etc. are the main source of data available for the reverse engineering of craniofacial tissues or organs through the rapid prototyping approach. These geometrical data can be conveniently elaborated through softwares such as Mimics, Rapidform, and Rhinoceros in order to define the CAD of the tissue to be restored. This CAD is converted in an igs and an stl

format in order to carry on simulation and CAM, respectively.

The advantage of this strategy is that the numerical model, characterised by finite elements developed through an automatic and/or guided mesh, can be calibrated and validated through experimental testing on solid models realised through CAM. Finally, the most suitable plan of the surgical treatment can be performed, such as the titanium bridge prosthesis obtained through milling (Figure 3).

Many works[24,38,39,48,50,101,107] have already reported examples of titanium-, ceramic- and acrylic-based implants manufactured by automated milling. However, often several geometrical forms cannot be milled because of their complexity. For this reason, if complex or overhanging structures need to be rebuilt, SL technique seems to represent an interesting solution[85,107]. Accordingly, particular geometrical structures and thinly tapered devices can be produced using the SL casting.

SL technique for cranioplasty was first used for manufacturing of titanium plates[64,104,105,107], and then PMMA-based prostheses[2,24,107].

As previously highlighted, several Carbon Fiber Reinforced Polymer (CRFC) implants have been designed, prepared and clinically tested since the 1980s[107]. These biocompatible implants biocompatible were radiolucent, heat-resistant, extremely strong, and light as its weight was 20% that of steel. Moreover, they showed elastic properties close to those of bone[86,107].

An original technique for manufacturing customized CFRP cranioplastic implants through SL technique was developed by Tomancok et al. (1997)[96] and the devices were then clinically tested[86,94,95].

The technology transfer of Solid Freeform Fabrication (SFF) to the biomedical field represents the key to produce customized devices[34,75,83]. SFF is a collective term for a group of technologies that can fabricate objects in a layer-by-layer fashion from the 3D computer design of the object. It was initially developed for fabricating prototype engineering parts, and, for this reason, the name “Rapid Prototyping” (RP) is also widely used[14,15,45,75,83,109]. Over the past years, more than 20 SFF technologies have been developed, differentiating themselves mainly by the method by which the layers are laid down, solidified, and attached to the previous ones[34,14,15,45,75,83,109].

Figures 4A and 4B show typical 3D printers used to directly fabricate solid models for biomedical applications from stl files.

The 3D photo printer (Figure 4A) realises the solid model by a layer below layer approach; during the process a plate moves in the upper direction, the gap is filled by the monomer and a projector provides the light to locally polymerise the resin. Instead, the inkjet printer manufactures the solid model through the layer on layer approach; a bed powder is locally consolidated by a binder, such as Poly-Vinyl-Alcohol (PVA) contained into a inkjet cartridge, hence the working plane moves in the bottom direction and a brush reports a film of fresh powder contained in a reservoir on the previously consolidated layer. The advantage of the former technology is that the entrapment of unreacted resin is avoided, as this resin comes out for gravity effects from the developing 3D solid. The main drawback is that a limited number of resins in combination with a photo-initiator system can be used. Moreover, for the photo-printing techniques, supports need to be properly designed in order to avoid debonding of the solid model from the moving plate.

Although there are several commercial variants of SFF technology that differ significantly in the way they build up 3D models, common features are also present as all SFF technologies are characterized by three basic steps in their process: data input, data file preparation, and object building[14,28,46,83]. In particular, the general process involves producing a computer-generated model using CAD software. The CAD model is expressed as a series of cross-sectional layers, and the data are implemented by the SFF machine, thus creating the physical model. Some SFF technologies require an additional step of post-processing in order to remove either temporary supports or the excessive material trapped inside the void space in the built structure. In addition, if a second type of data source is data obtained from computed tomography or magnetic resonance imaging medical scans can be used to manufacture a customized CAD model that should be characterized by the exact external shape required to correct the damaged tissue site[9,28,34,46,83].

Among the rapid prototyping techniques, 3D printing incorporates a technology to eject a binder from a jet head that moves in accordance with the CAD data, onto a polymer powder surface. Basically, the binder dissolves and joins adjacent powder particles. The piston chamber is lowered and refilled with another layer of powder and the process repeated. The unbound powder acts to support overhanging or unconnected features and needs to be removed after component completion[9,34,83].

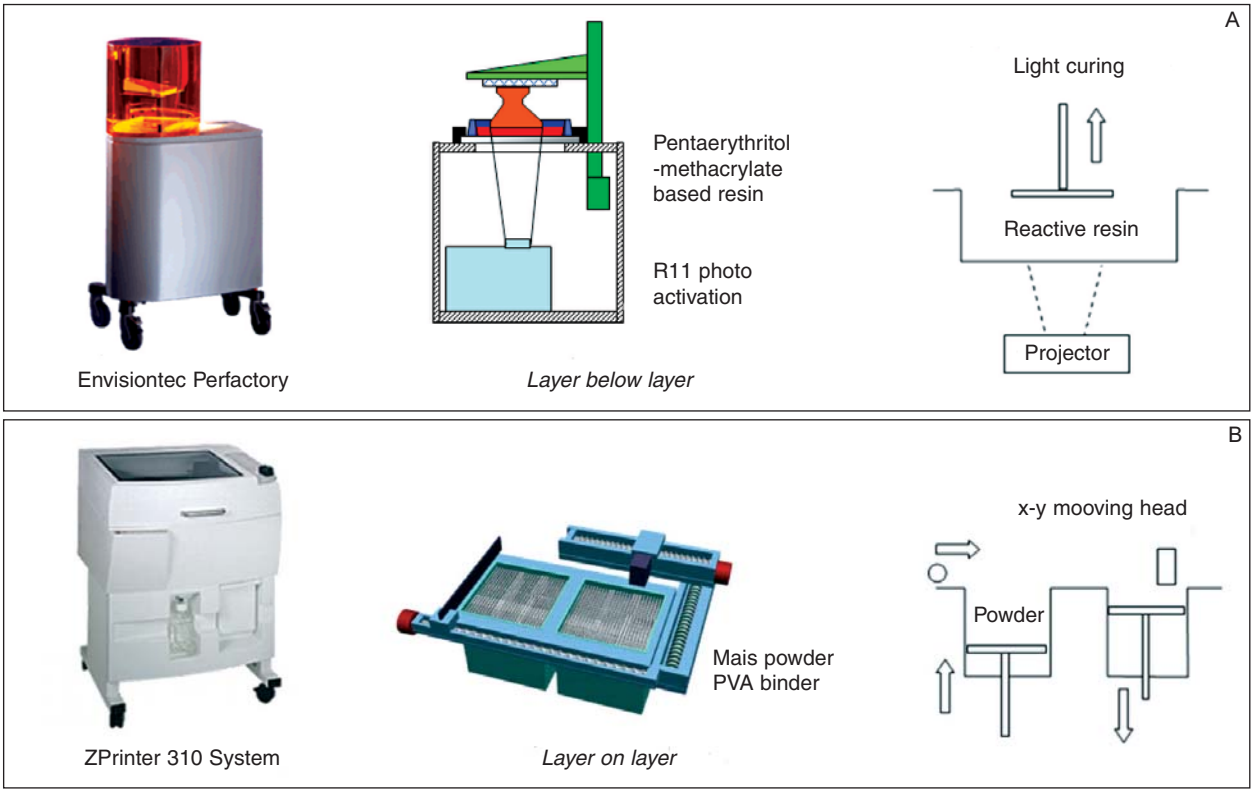

Figure 4. 3D printers: photo printer (A); ink-jet printer (B). Legend: PVA =Poly-Vinyl-Alcohol.

In this context, an example of a polymer-based custom-made skull model with a large defect was obtained through a 3D printer (ZPrinter®) by integrating the reverse engineering approach and the rapid prototyping technique (Figure 5).
The custom-made skull model was designed and manufactured by using mais powder and PVA as polymeric binder, following several basic steps.
3D scanning was performed through a Cyberware Mini Shop Model scanner, in order to capture the image and, hence, shape and size of the natural skull.
The point clouds produced by 3D scanners were not used directly, whilst NURBS (Non Uniform Rational B-Splines) surface models and editable feature-based CAD models were considered.
The process of converting a point cloud into a usable 3D model is called "reconstruction" or "modelling". Consequently, the 3D model of the human skull was then reconstructed using dedicated software, such as Materialise Mimics, Magics and Rapidform, thus creating the NURBS that describe the 3D complex anatomical geometry.

☐ SCAFFOLDS FOR CRANIOFACIAL TISSUE ENGINEERING

Tissue engineering has been defined as a multidisciplinary field that integrates principles of engineering and life sciences to develop biological substitutes that restore, maintain or improve tissue function[58].
Tissue engineering approach to craniofacial skeletal reconstruction evokes the general principles of using porous scaffolds that may be seeded with cells and may deliver biofactors to regenerate the natural tissue[41,42].
This indicates that craniofacial tissue engineering promises the regeneration or de novo formation of craniofacial, dental, oral structures lost as a consequence of trauma, congenital anomalies, and diseases. Accordingly, several craniofacial structures (i.e., mandibular condyle, calvarial bone, cranial suture, and subcutaneous adipose tissue) have been already engineered using mesenchymal stem cells, growth factor, and/or gene therapy approaches[65].
Craniofacial scaffolds have to satisfy the typical requirements for mechanically functioning tissues of enhancing tissue regeneration through biofactor de-

livery while maintaining their temporary mechanical function as support until the neo-formed tissue can bear load[41,42]. Furthermore, craniofacial scaffolds must reproduce very complex 3D anatomic defects.
Clearly, an engineering process that has to satisfy all the above mentioned requirements should be able to finely control scaffold exterior shape as well as the inner porous architecture.
Over the last two decades, the development of novel scaffold materials based on the cell guidance concept was also proposed benefiting from contemporary advances in the fields of molecular biology and materials science[33].
With regard to synthetic polymers, aliphatic polyesters such as Poly-Glycolic-Acid (PGA), Poly-Lactic-Acid (PLA), their copolymers such as Poly-Lactic-*co*-Glycolic Acid) (PLGA) and Poly-CaproLactone (PCL) are the most commonly used polymers for fabricating scaffold[34]. The products obtained from the degradation of these can be removed by natural metabolic pathways.
Furthermore, the concept of polymer-based composite material has been rapidly extended to the design of multifunctional scaffolds for tissue engineering.
Several polymeric and composite materials have been considered to make porous scaffolds, using both conventional (i.e., gas foaming, solvent casting/particulate leaching, phase separation, melt molding, freeze drying, solution casting, and emulsion freeze drying) and more advanced manufacturing methods (i.e., rapid prototyping techniques)[33].
Among these SFF technologies, many have been modified or developed towards the manufacturing of tissue engineering scaffolds, including 3D printing, fused deposition modeling, ink-jet printing, stereolithography, selective laser sintering and a few other extrusion-based technologies, such as 3D bioplotting[9,33,44,56,57,91].
As already know, rapid prototyping techniques offer the possibility of directly fabricating scaffolds with different geometric structures and with different properties. The scaffolds are built layer-by-layer through material deposition by CAD/CAM techniques, such as a molten thermoplastic material, as in the case of the fused deposition modeling technique, or as droplets together with a binding agent, as in the 3D printing technique[34].
Among all of the rapid prototyping techniques, 3D plotting[56,57] and 3D fiber deposition[34,55,62,69,70,106] have been recently developed and used for manufacturing scaffolds. In particular, 3D fiber deposition may be considered as a modified technique of 3D plotting for the extrusion of highly viscous polymers, and it is a fused deposition technique in which a molten polymer is extruded and then deposited through a servo-mechanically controlled syringe that applies pressure. This process allows the fabrication of scaffolds with specific shape and size and 100% interconnectivity. By using these CAD/CAM techniques, the scaffolds obtained possess a defined structure and architecture, and can be built with a customized shape.
The key element of the 3D fiber deposition technique is a dispensing machine known as a Bioplotter that was initially developed to manufacture scaffolds from hydrogels for soft tissue engineering[56,57].
However, composite materials consisting of polymers reinforced with inorganic ceramic fillers have attracted research interest also in the field of tissue engineering to reconstruct several hard mineralized tissues, such as bone. Many studies have demonstrated the significant role of nanotechnology in improving the efficacy of polymeric materials for bone regeneration[33].
Nanocomposites can mimic the constituents of natural bone better than the individual components, and the effect of nanoscale features on scaffold function becomes important. Accordingly, with regard to craniofacial tissues, PCL/HA nanocomposite scaffolds for human mandibular symphysis and ramus tissue engineering were designed and manufactured by integrating different techniques such as 3D scanning,

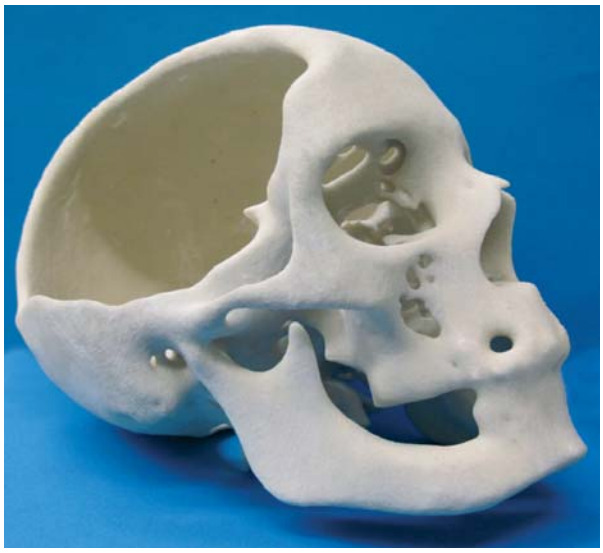

Figure 5. Image of a polymer-based custom-made skull model with a large defect obtained using a 3D printer (ZPrinter®).

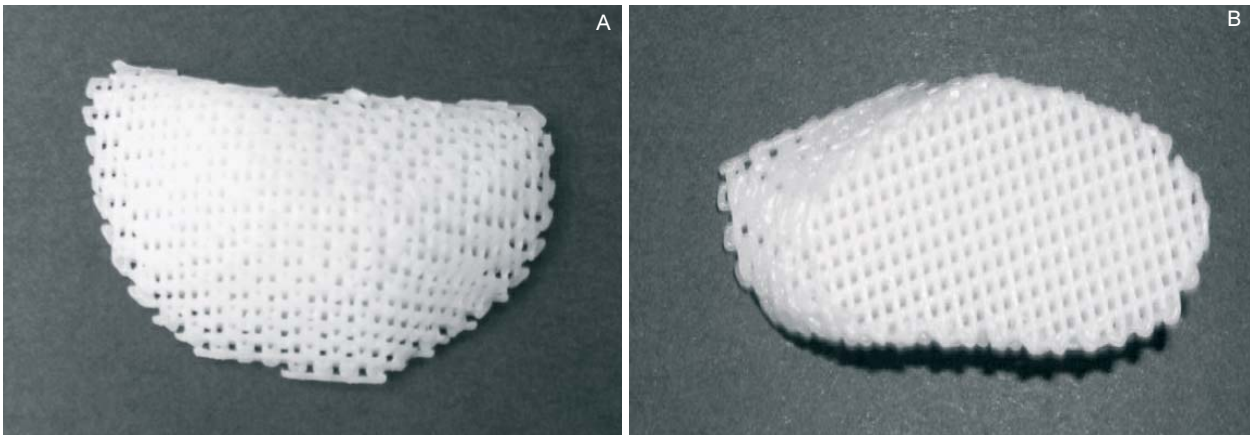

Figure 6. Polycaprolactone/hydroxyapatite nanocomposite scaffolds for mandibular symphysis (A) and ramus portion (B) tissue engineering.

3D modelling and 3D fiber deposition technique, with those related to the preparation of PCL/HA nanocomposite material for scaffolds processing.
Images of customized PCL/HA nanocomposite scaffolds for human mandibular symphysis and ramus tissue engineering are reported in Figure 6.
Clearly, approaches in scaffold design must be able to create hierarchical porous structures to obtain desired mechanical function and mass transport (permeability and diffusion) properties[41,42]. This means to understand how well the scaffold could meet conflicting mechanical function and mass transport needs.
Material chemistry and surface topography determine the maximum functional properties that a scaffold can achieve, as well as how cells interact with it. On the other hand, a porous scaffold structure is needed because of mass transport requirements for cell nutrition, porous channels for cell migration. Benefiting from this, a topological optimization is required and several approaches actually compute new microstructures to obtain the desired properties. These approaches have either been considered to optimize functional elastic properties with a constraint on porosity, or to maximize permeability with a constraint on desired elastic properties and permeability[41,42].

□ CONCLUSION AND FUTURE TRENDS

Several kinds of non-degradable biomaterials such as polymers (i.e., PMMA), ceramics, composites, titanium and metal alloys still represent the most used prosthetic approach to clinically restore a hard craniofacial tissue defect. Although the primary stability of these biomaterials is generally achieved quicker than other approaches involving biodegradation and tissue regeneration, the long-term stability represents the main limitation for structural craniofacial applications. Therefore, the research on this topic is almost focused on the development of materials and technologies in order to design prostheses combining several properties such as high biocompatibility, tailored biomechanical properties, high strength and toughness, resistance to impact, to abrasion and to corrosion, fatigue resistance, adequate transparency to electro-magnetic waves for diagnostic purposes, lightness of massive prostheses. Moreover, the interface between synthetic non-degradable materials and craniofacial tissues represents an important research topic, as this is the weakest region of the engineered design. On the other hand, the complexity of properties combination increases as the design deals with degradable materials to make scaffolds for craniofacial tissue regeneration. In fact, these materials require multifunctional properties in order to provide a suitable cell-material interaction capable to account for cell attachment, migration, proliferation and differentiation. Also, programmed biomechanical properties need to be satisfied for the regeneration of craniofacial bone tissues; the load bearing function has to be transferred from the engineered material to the growing tissue. The rapid prototyping approach seems to be a promising technology to manufacture a custom made scaffold satisfying the macro geometry of the craniofacial defect, and simultaneously providing a reproducible and fully interconnected architec-

ture at the meso and micro scales. Both in vitro cell cultures using bioreactors and implantation of cell-scaffold constructs represent

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