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(54) Title: PROCESS FOR PREPARING CERAMIC IMPLANTS FOR MEDICAL PURPOSES

(57) Abstract: A process for manufacturing a ceramic implant with a surface which forms a permanent bonding to bone cell tissues, the surface providing improved osseointegration, the process comprising the step of: - a pretreatment of the ceramic material with the surface wherein said surface of the ceramic material is exposed to a conditioning plasma, which is produced by means of direct current (DC) or alternating current (AC), such as high or radio frequency (HF, RF), or microwaves (MW) at a low pressure, followed by a second step; - a treatment with a reactive plasma in which an organic compound is added to the plasma for the at least partial application of an organic phase to said surface wherein the organic compound is selected from the group consisting of aliphatic amines, cyclic amines, unsaturated and aromatic amines as well as combinations thereof.



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Process for Preparing Ceramic Implants for Medical Purposes

The present invention is related to a preparation process of ceramic implants for medical purposes having a surface that forms a permanent bond to cell tissues, especially bone cells, to an implant obtainable by the process according to the invention, and to the use of the implant according to the invention.

The design of ceramic surfaces in implants, especially dental implants, is still in its beginnings in contrast to metallic implants. Commercially available products are mostly roughened by sandblasting and ensure thus a better mechanical anchoring in the cell tissue in comparison to smooth surfaces. However, they require relatively long times for osseointegration compared to the highly developed surfaces of titanium implants,. Thus, in combination with one-part ceramic implants as usual today, there is an additional risk in the osseointegration of these implants.

The sandblasted surface is non-optimal for the interface between the ceramic and the surrounding bone.

This disadvantage could be eliminated by the wet-chemical application of polymers such as polyallylamine or proteins or matrix molecules, such as collagens, fibronectin or osteonectin. However, these tend to adhere poorly to the exposed surfaces of the implants, and an early interface fracture may occur. When cell-side stimulants (e.g., BMPs or interleukins) are employed, the products cannot be sterilized because of the thermolability of the proteins, and thus are hardly suitable for clinical use in implantology.

US-A-2009/01766191 discloses the coating of ceramic surfaces with a thin titanium film. However, no information is given about the durability of the adhesion of this layer, and the advantage of metal-free ceramics as an implant material is thwarted.

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WO-A-2001/1019323 describes a coating process of Mg-stabilized zirconia ceramic, which is unsuitable for bone contact. Moreover, the ceramic must have a roughness of less than 10 nm as a precondition.

5 US-A-4,757,014 discloses a plasma treatment of plastics in order to apply thereto first a layer of a polymer or a silane-functionalized compound for protein immobilization, and thereafter a biologically active protein. The plasma treatment is carried out with a radiofrequency plasma (10-125 kHz) at 10 mTorr to 10 Torr (low pressure to atmospheric pressure) in air, oxygen, carbon dioxide, argon, helium, nitrogen oxides or water vapor to produce functional groups for the immobilization
10 of biologically active proteins and enzymes.

Coatings on the ceramic as described in GB-A-2 407 523 do not solve the problem of an improved contact formation between cells and the grafted implant sufficiently either. In this patent, ceramic-like coatings are applied by means of plasma spraying, vacuum plasma spraying, air plasma spraying or high-velocity oxygen
15 fuel (HVOF) coating.

WO 01/85635 A discloses a method of coating the surface of an inorganic substrate of glass, silicon dioxide, ceramics or carbon, which method includes a step of cleaning the surface of the substrate by subjecting the surface to a reducing gas plasma, a step of activating the surface by generating radicals on the surface of
20 the substrate by subjecting the surface to a reducing gas plasma and forming a first layer on the substrate surface using a plasma enhanced polymerization process employing one or more monomers comprising monomers with a sufficient low molecular weight for them to be in their gaseous state in the gas plasma, selected from the group consisting of C₁-C₁₆ alkanes, C₂-C₁₆ alkenes, C₂-C₁₆
25 alkynes, , styrene, aromatic monomers of styrene compounds, monomers of vinyl- and acrylate-compounds.

WO 2009/103775 A discloses a method for the coating of a surface of a ceramic basic body with a titanium compound, comprising the steps of (i) providing a preformed ceramic material; (ii) at least one step of surface activation of said
30 ceramic material using a plasma for plasma-chemical surface preparation

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wherein the plasma comprises high-energy ions; (iii) at least one step of applying a titanium compound bonding layer to said ceramic material by plasma-supported coating wherein the plasma-supported coating is performed in pulsed and/or non-pulsed version; (iv) at least one step of applying a functional titanium compound layer by pulsed plasma-supported coating.

CH 702 731 A is related with fabricating a part comprising a substrate and an elastomeric coating, comprises: (a) optionally, treating the substrate to generate active groups on surface; (b) applying to the substrate a first composition comprising at least a first elastomeric material, at least one silane and optionally at least one bonding agent to form an intermediate layer; (c) applying a second composition comprising a second elastomeric material to form the coating; and (d) annealing the formed part.

The production of chemically reactive surfaces with plasma polymers [K.S. Siow, L. Britcher, S. Kumar, H.J. Griesser, Plasma Process. Polym. 3 (2006), 392-418] is substantially more suitable. This review mainly describes radiofrequency (RF) excited plasmas (10 kHz to 1 MHz) in the low-pressure region for producing coatings having a thickness of 50-500 nm. Alternatively, microwave plasmas (1 MHz to 20 GHz) may also be used for this purpose [Finke, B.; Lüthen, F.; Schröder, K.; Mueller, P.D.; Bergemann, C.; Frant, M.; Ohl, A.; Nebe, J.B. Positively charged plasma polymerized titanium boosts osteoblastic focal contact formation in the initial adhesion phase, Biomaterials 28 (2007), 4521-4534].

Puleo DA et al report in Biomaterials 2002 May;23(9):2079-87 that immobilization of biomolecules on surfaces enables both localization and retention of molecules at the cell-biomaterial interface. Since metallic biomaterials used for orthopedic and dental implants possess a paucity of reactive functional groups, biomolecular modification of these materials is challenging. In the present work, they investigated the use of a plasma surface modification strategy to enable immobilization of bioactive molecules on a "bioinert" metal. Conditions during plasma polymerization of allylamine on Ti-6Al-4V were varied to yield 5 ("low")- and 12 ("high")-NH₂-groups/nm². One- and two-step carbodiimide schemes were used to immobilize lysozyme, a model biomolecule, and bone morphogenetic protein-4 (BMP-4) on the

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aminated surfaces. Both schemes could be varied to control the amount of protein bound, but the one-step method destroyed the activity of immobilized lysozyme because of crosslinking. BMP-4 was then immobilized using the two-step scheme. Although BMP bound to both low- and high-NH₂ surfaces was initially able to induce alkaline phosphatase activity in pluripotent C3H10T1/2 cells, only high amino group surfaces were effective following removal of weakly bound protein by incubation in cell culture medium.

However, the adhesion of thus prepared coatings on titanium is rather poor. Ceramic surfaces have a similar behavior. The adhesion forces are further reduced because of the high mechanical material differences between the ceramic substrate and the polymer-like coating, which results in a more reduced layer adhesion.

An object of the present invention is to provide a process for preparing an implant that ensures improved healing and osseointegration.

The object of the present invention is achieved by a process for manufacturing a ceramic implant with a surface which forms a permanent bonding to bone cell tissues, the surface providing improved osseointegration, the process comprising the step of

- a pretreatment of the ceramic material with the surface wherein said surface of the ceramic material is exposed to a conditioning plasma, which is produced by means of direct current (DC) or alternating current (AC), such as high or radio frequency (HF, RF), or microwaves (MW) at a low pressure, followed by a second step which is
- a treatment with a reactive plasma in which an organic compound is added to the plasma for the at least partial application of an organic phase to said surface wherein the organic compound is selected from the group consisting of aliphatic amines, cyclic amines, unsaturated and aromatic amines as well as combinations thereof.

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According to the invention, the plasma is produced by means of direct current (DC) or alternating current (AC), such as high or radio frequency (HF, RF), or microwaves (MW) at a low pressure, typically 0.1 Pa to 0.9 kPa. The present invention includes MW and RF plasmas at pressures of from 100 kPa to 500 kPa (normal pressure range).

In one embodiment of the process according to the invention, the plasma may be employed under inert gas, or with admixture of oxygen, hydrogen, water, hydrogen peroxide.

The ceramic materials forming the ceramic implant which can be used in the process according to the invention are selected, in particular, from the group consisting of leucite-containing or leucite-free oxide ceramic, feldspar ceramic.

According to the process of the invention, the organic phase can be formed from the organic compound selected from the group consisting of aliphatic amines, cyclic amines, unsaturated and aromatic amines as well as combinations thereof. The organic compounds may be, in particular, ethylene diamine, heptylamine, diaminopropane, (substituted) cyclopropylamines, diaminocyclohexanes, allylamine, dimethylformamide, nitrogen-containing heterocycles, such as azirines, pyrroles, pyridines, piperidines or pyrrolidines.

The present invention relates to a ceramic implant obtainable by the process according to the invention, and to a ceramic implant provided with at least partial coating by an organic phase. Said ceramic implant provided with at least partial coating by an organic phase has an organic phase with a thickness of from 1 nm to 10 μ m. The coating is advantageously resistant to external mechanical stress, in particular, scratch-resistant. The coating is advantageously stable over the time frame of one year in its adhesiveness.

The present invention relates to an implant material having a scratch-resistant at least partial coating of an organic phase.

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The present invention also relates to the use of said ceramic implant, especially in the orthopedic or dental field.

Plasmas suitable for creating an interface for functionalization in accordance with the process according to the invention include the following, in particular:

- 5 DC or HF plasmas (high frequency plasmas, including RF and microwave plasmas, 0 Hz to 10 GHz) in the low pressure range, i.e., from 10^{-1} Pa to 1 kPa, preferably around 10 Pa to 1 kPa, which are inductively and/or capacitively coupled. The plasmas may also be pulsed with duty cycles (the ratio of plasma on times to the duration of the period) of from 10^{-6} to 0.9, advantageously from 0.05 to 0.5, more
10 suitably from 0.1 to 0.3. Normal pressure plasmas, such as barrier discharges, which have at least one dielectric barrier in the discharge space or are performed as coplanar discharge, may also be employed. The operating frequency of the applied (pulsed) alternating voltage is from 50 Hz to 500 kHz at voltages within a range of from 1 to 10 kV. Further, plasma jets are suitable. This term refers to
15 plasma sources in which the plasma produced is blown by the current of working gas employed out of an opening into the surrounding space. They can be operated with pulsed direct voltage (1 to 15 kV at 10 to 25 kHz), MF (1 to 5 kV at 50 kHz) or microwaves (e.g. 1 – 10 GHz), as well as HF (e.g. 1 – 50 MHz). In this method, the plasma burns at an operating pressure of from 1 to 10^5 Pa. The process
20 according to the invention can employ plasmas in inert gases, but admixtures of oxygen, hydrogen, water, hydrogen peroxide are also possible. The plasmas may also burn within the latter as pure substances.

A correspondingly suitable plasma pretreatment yields a surface having a carbon content of < 25 % (XPS (X-ray photoelectron spectroscopy) measurement),
25 preferably < 20 % (XPS measurement). The surface has chemically reactive oxygen-containing groups and free radicals, enabling a permanent bond to the nitrogen-containing functionalization.

In one embodiment, this plasma step can be directly combined with a second plasma step in one reactor without intermediate aeration. Thus, the corresponding
30 plasma designed for a pretreatment is applied to the ceramic surface until the

carbon content of typically 35-80% (XPS measurement), which corresponds to a C/Zr ratio of 1.5-20 in the case of YSZ (yttria-stabilized zirconia), has been reduced to values below 25%, preferably < 20%, which corresponds to a C/Zr ratio of < 1.3, preferably < 0.8, in the case of YSZ (yttria-stabilized zirconia).

5 Without being limited to such explanation or to the hypothesis underlying the explanation, the process according to the invention for functionalization yields a firmly adhering, long-term water-stable functionalization of the surface, which includes introduced amino groups, in particular, and can cause adsorption of glycoproteins from the biological environment in which the implant is placed. The
10 deposition of glycoproteins to the implant surface is one of the first steps of osseointegration. The process according to the invention enables functionalization, so that the roughness necessary for mechanical anchoring and other material properties important for the bond between the tissue and implant are retained.

In one embodiment of the process according to the invention, the plasma acts in
15 the presence of nitrogen, ammonia and/or at least one nitrogen-containing, especially organic, compound on the surface of the ceramic implants.

According to the invention, at least one nitrogen-containing organic compound is selected from the group of aliphatic amines, cyclic amines, unsaturated amines and aromatic amines. Thus, in particular, the following substances may be
20 mentioned in an exemplary way: ethylene diamine, heptylamine, diaminopropane, (substituted) cyclopropylamines, diaminocyclohexanes, allylamine, dimethylformamide, nitrogen-containing heterocycles, such as pyrroles.

Typically, the plasma is a microwave plasma, a DC or RF plasma (radio frequency, 0 Hz to 10 GHz) in the low pressure range, i.e., from 0.1 Pa to 1 kPa, preferably
25 around 10 Pa to 1 kPa. The coupling of the energy may be effected inductively and/or capacitively. The plasma should advantageously be pulsed with duty cycles of from 10^{-6} to 0.9, advantageously from 0.05 to 0.5, more suitably from 0.1 to 0.3. Normal pressure plasmas, such as barrier discharges, which have at least one dielectric barrier in the discharge space or are performed as coplanar discharge,
30 may also be employed. The operating frequency of the applied (pulsed) alternating

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voltage is from 50 Hz to 500 kHz at voltages within a range of from 1 to 10 kV. Further, atmospheric plasma jets are suitable. This term refers to plasma sources in which the plasma produced is blown by the working gas flow expending from the jet nozzle into the surrounding space. They can be operated with pulsed direct
5 voltage (1 to 15 kV at 10 to 25 kHz), MF (1 to 5 kV at 50 kHz) or microwaves (1 – 10 GHz), as well as HF (1 – 50 MHz). In this method, the plasma burns at operating pressures of from 1 Pa to 10^5 Pa. Preferably, anisothermic plasmas may be applied.

10 Upon contact with the implants prepared according to the invention, proteins adsorb and cells respond with a significantly improved initial attachment. In cell spreading, visibly intensified cell spreads as compared to untreated surfaces could be detected, also in the adhesion of the cells, which literally merge into the substrate topography.

15 This results in a significant shortening of the osseointegration time, and in addition, the mentioned functionalization is resistant to sterilization and long time stable.

In one embodiment, the ceramic implant according to the invention has an organic substrate on its surface, especially in a substantially uniform thickness of from 0.1 to 15 nm, preferably from 1 to 10 nm.

20 In a specific embodiment, the biologically active surface is applied in a high vacuum plasma reactor, i.e., to the implants that have already been morphologically structured. The high vacuum plasma reactors may be either microwave (MW, 2.45 GHz), radio frequency (RF, 13.56 MHz or 27.12 MHz) parallel plate reactors or inductively coupled plasmas (ICP reactors, 13.56 MHz or 27.12 MHz). The electric
25 power is coupled, for example, at a low pressure (typically from 0.1- 1 kPa), whereby a plasma is ignited and maintained for some time. The process sequence typically consists of two parts:

1. Exposure to a conditioning plasma in the presence of argon, oxygen, nitrogen, air, carbon tetrafluoride, or mixtures thereof for a sufficient time to activate the

surface. The corresponding duration is known to the skilled person and is usually from 10^{-3} to 10^3 s, preferably from 1 s to 100 s.

2a. A reactive plasma in which biologically active surfaces are produced by maintaining plasmas in aliphatic amines (such as ethylene diamine, heptylamine, diaminopropane), cyclic amines (such as cyclopropylamine, diaminocyclohexanes) or unsaturated amines (such as allylamine) (further examples, see above) with or without inert gas dilution (Ar, He, Xe) with or without admixing reactive gases (NH_3 , N_2 , air) with nitrogen-containing molecules, such as nitrogen and/or ammonia.

2b. Alternatively, aliphatic hydrocarbons (methane, ethane, propane, n-butane, isobutane), unsaturated hydrocarbons (ethylene, acetylene, propylene, butadiene), cyclic hydrocarbons (cyclopropane, cyclohexane) or aromatic hydrocarbons (benzene, toluene) may also be employed with or without inert gas dilution and with or without nitrogen-containing admixtures, such as ammonia (NH_3), hydrogen or amines. Thus, carbon surfaces may also be produced and subsequently activated with nitrogen-containing plasmas (N_2 , NH_3 , H_2 or amines).

In another embodiment of the process according to the invention, the implants with the ceramic surface were attached to a motor by means of a receptor means, and rotated. A plasma jet operated in argon (1.1 MHz) is scanned over the implants with or without admixture of oxygen in such a way that the entire length is activated. Any admixing of oxygen is stopped, and thereafter, the conditioning is effected by admixing aliphatic amines (e.g., ethylene diamine, heptylamine, diaminopropane), cyclic amines (e.g., cyclopropylamine, diaminocyclohexanes), or unsaturated amines (e.g., allylamine).

The invention is further illustrated by means of the following examples.

Example 1:

The biologically active surface is applied in a vacuum plasma reactor to the implants that have already been morphologically structured. The vacuum plasma

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reactor V55G (Plasma-finish, Schwedt, Germany) is made of aluminum and has dimensions of 40 x 45 x 34 cm³ (width x depth x height). The plasma is ignited by means of a microwave plasma source (microwave, MW, 2.45 GHz), which couples its power into the reactor through a microwave parabolic mirror. The implants are kept in a rotation means that causes rotation of the implants in the reactor both at 8 revolutions/min and at 120 revolutions/min about their own axis.

For conditioning the implant surfaces, the reactor is first evacuated to 6 Pa, followed by introducing an oxygen/argon mixture with flow rates of 100 sccm O₂ and 25 sccm Ar (sccm = standard cubic centimeters per minute), which is stabilized at 0.5 mbar within one minute. With a microwave power of 500 W, a continuous (cw) plasma is ignited for one minute at the mentioned parameters (50 Pa, 100 sccm O₂, and 25 sccm Ar). Subsequently, the mixture of gases is pumped off (6 Pa). The samples remain under vacuum.

On the implants, a surface has formed that lead to a very strong adhesion of the subsequent biologically active finishing of the surface.

For biologically active conditioning, a mixture of argon (50 sccm) and allylamine (1.5 ml/15 min, i.e., 100 µl of liquid/min) is adjusted. After a period of one minute, the MW plasma (2.54 GHz) with a power of 500 W is ignited and pulsed (300 ms on, 1700 ms off) for 240 s (24 s effectively). Thereafter, the mixture of gases is pumped off, and the reactor is aerated with nitrogen.

Example 2:

Two types of ceramic surfaces differing in their roughness were applied. The root-mean-squared-roughnesses R_q are 294±3 nm and 747±42 nm determined with the profiler Dektak 3ST (Veeco, St. Barbara, USA, radius of the standard diamond stylus 2.5 µm, stylus force 30 mg, scan length 500 µm; 100 measurements/sample at 500 µm length at 3 sample of one charge). At first, the surfaces were exposed to a Ar/O₂ - conditioning plasma (micro wave, 2,45 GHz, 500 W, 50 Pa, 60 s) followed by the treatment with the reactive plasma (microwave, 2,45 GHz, 500 W, 50 Pa, 144 s effective) in the presence of the precursor al-

ylamine for generation of a bioactive surface. By XPS surface analyses (results shown in Fig. 1A und B) elevated nitrogen content was detected expressed as N/C-ratio between 25 and 30 %. The density of the amino groups NH_2/C on the surface was 2-3 %.

5 Fig. 2A-D show the behaviour of cells when contacted with the surface treated according to example 2. For morphological cell observations human osteoblast-like cells (cell line MG-63, ATCC, CRL-1427, LGC Promochem, Wesel, Germany) were cultured in Dulbecco's modified Eagle's medium, serum-free, 1% gentamicin from Ratiopharm GmbH, Ulm, Germany at 37°C in a humidified atmosphere with 5%
10 CO_2 on the untreated as well as modified ceramic surfaces for 24 h, fixed with 4% glutaraldehyde (1 h), dehydrated through a graded series of acetone, dried in a critical point dryer (K 850, EMITECH, Taunusstein, Germany), sputtered with a coater (SCD 004, BAL-TEC, Balzers, Lichtenstein) and observed in the scanning electron microscope (SEM, DSM 960A, Carl Zeiss, Oberkochen, Germany).

15 Example 3:

Two types of ceramic surfaces differing in their roughness were applied. The root-mean-squared-roughnesses R_q are 294 ± 3 nm and 747 ± 42 nm determined with the profiler Dektak 3ST (Veeco, St. Barbara, USA, radius of the standard diamond stylus 2.5 μm , stylus force 30 mg, scan length 500 μm ; 100 measure-
20 ments/sample at 500 μm at 3 sample of one charge). The surfaces were exposed to an Ar/O_2 normal pressure plasma (HF, 1 MHz, 10 W, 100 kPa, 120 s) and a bioactive surface was generated. A C/Zr-ratio of < 1.3 was found by XPS analyses. The results are shown in Fig. 3A und B.

Fig. 4A-D show the behaviour of cells when contacted with the surface treated
25 according to example 3. The osteoblast cultivation on the ceramic samples, the preparation and the finally observation using SEM is already described above (Fig. 2).

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C L A I M S :

1. A process for manufacturing a ceramic implant with a surface which forms an initial and a permanent bonding to bone cell tissues, the surface providing improved osseointegration, the process comprising the step of
 - 5 - a pretreatment of the ceramic material with the surface wherein said surface of the ceramic material is exposed to a conditioning plasma, which is produced by means of direct current (DC) or alternating current (AC), such as high or radio frequency (HF, RF), or microwaves (MW) at a low pressure, followed by a second step;
 - 10 - a treatment with a reactive plasma in which an organic compound is added to the plasma for the at least partial application of an organic phase to said surface wherein the organic compound is selected from the group consisting of aliphatic amines, cyclic amines, unsaturated and aromatic amines as well as combinations thereof.
- 15 2. The process according to claim 1, wherein MW and RF plasmas are produced at pressures of from 100 kPa to 500 kPa (normal pressure range).
3. The process according to claim 1 or 2, wherein said plasma is employed under inert gas, or with admixture of oxygen, hydrogen, water, hydrogen peroxide.
- 20 4. The process according to at least one of claims 1 to 3, wherein said ceramic materials are selected from the group consisting of leucite-containing or leucite-free oxide ceramic, feldspar ceramic.
5. The process according to at least one of claims 1 to 4, wherein said organic compounds are ethylene diamine, heptylamine, diaminopropane, (substitut-
25 ed) cyclopropylamines, diaminocyclohexanes, allylamine, dimethylformamide, nitrogen-containing heterocycles, such as azirines, pyrroles, pyridines, piperidines or pyrrolidines.

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6. A ceramic implant provided with an organic phase obtainable by the process according to at least one of claims 1 to 5.
7. The ceramic implant according to claim 6 provided with an at least partial coating by an organic phase having a thickness of from 1 nm to 10 μm .
- 5 8. The ceramic implant according to claim 6 or 7 having a density of amino groups on its surface of 1-8 % NH_2/C , determined by XPS measurements.
9. The material according to at least one of claims 6 to 8 provided with an at least partial coating by an organic phase that is resistant to external mechanical stress.
- 10 10. Use of the ceramic implant according to at least one of claims 6 to 9 as an implant, especially in the orthopedic or dental field.

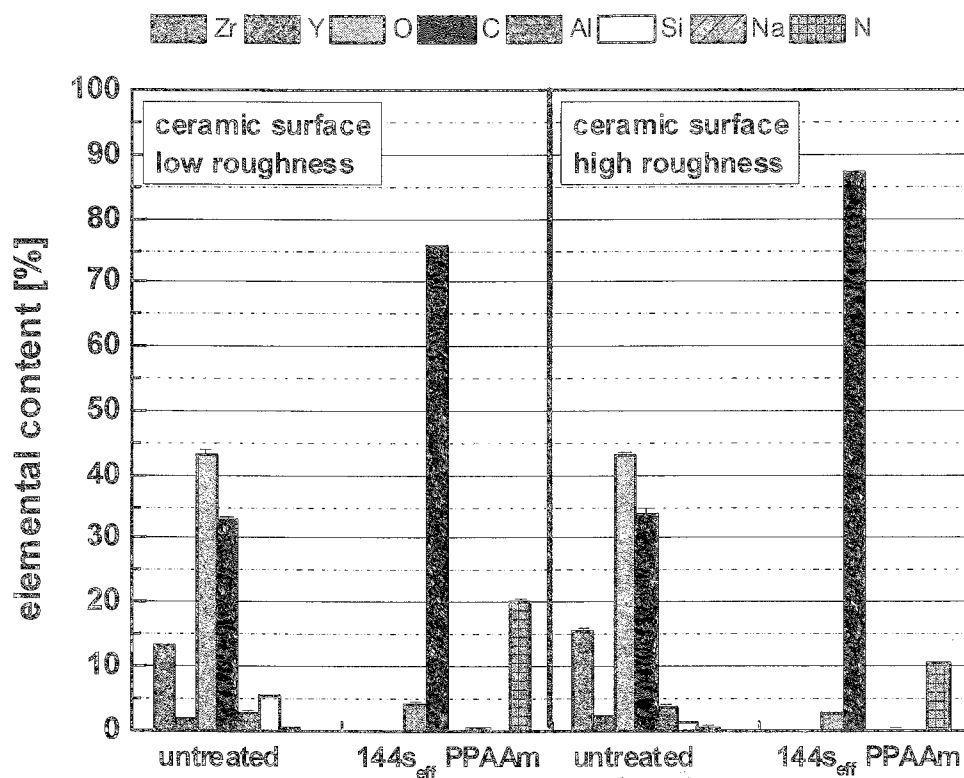
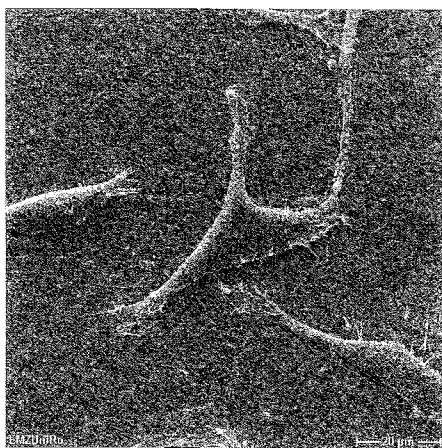


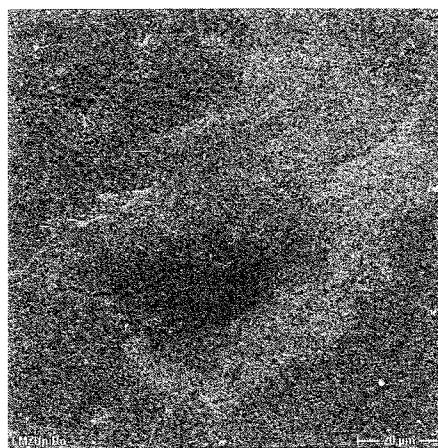
Fig. 1A

Fig. 1B

untreated ceramic surface



PPAAm treated ceramic surface



ceramic surface with low roughness

Fig. 2A

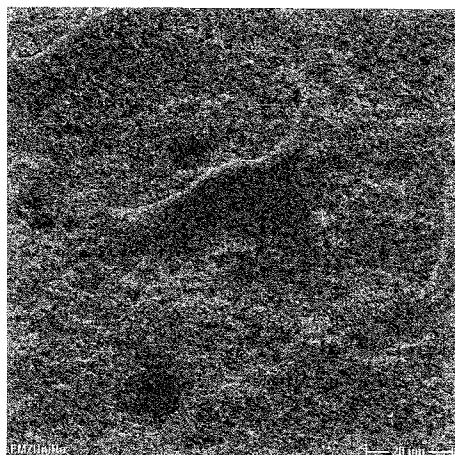
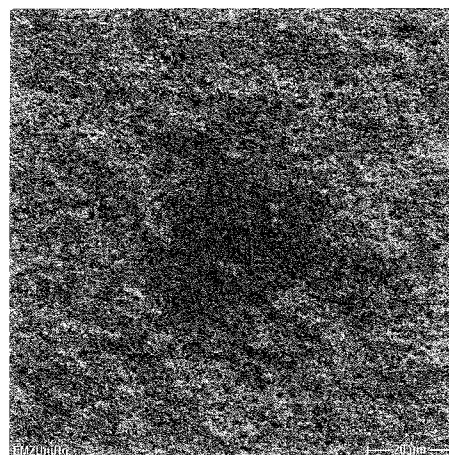


Fig. 2B



ceramic surface with high roughness

Fig. 2C

Fig. 2D

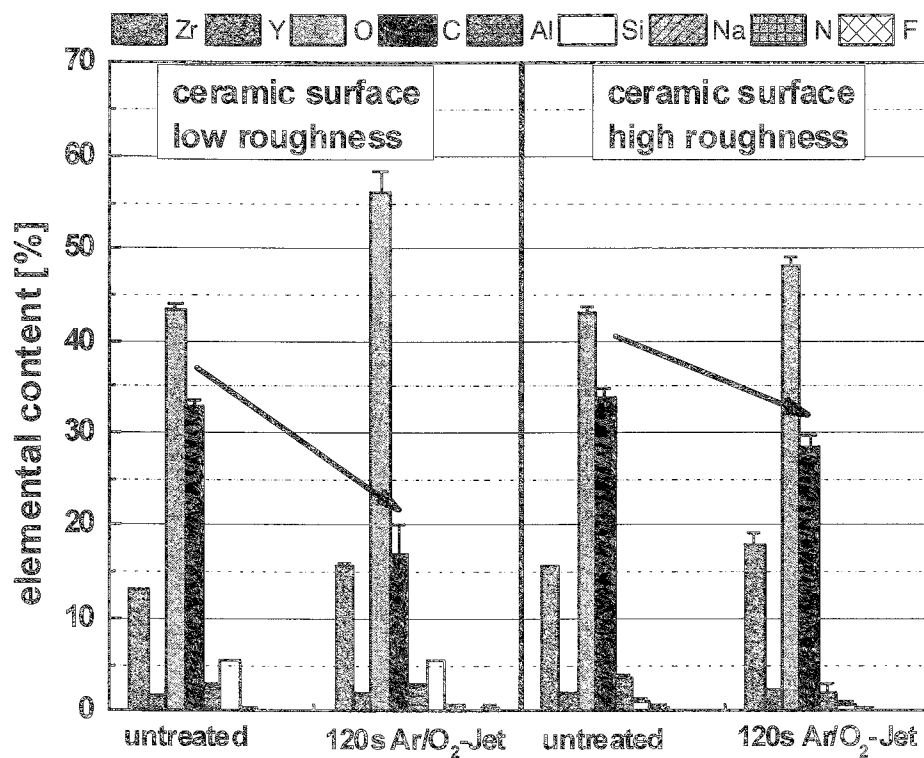
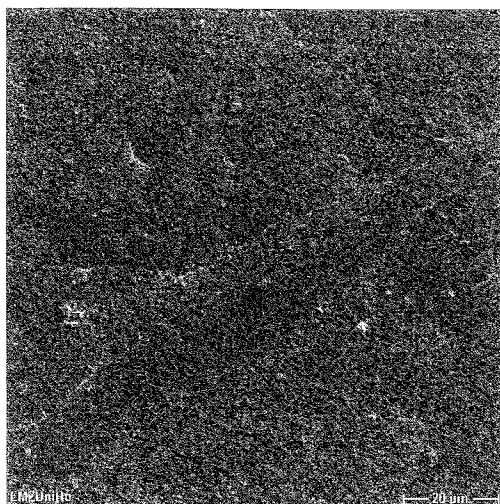


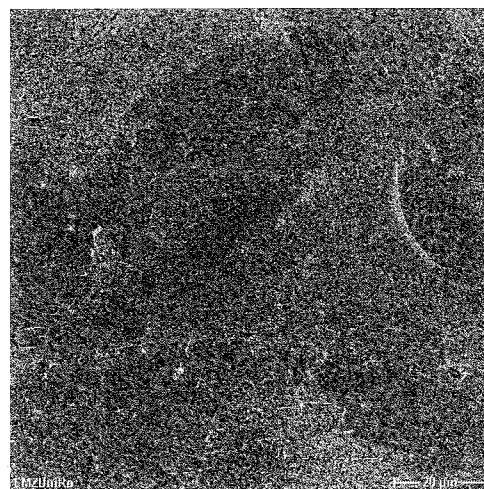
Fig. 3A

Fig. 3B

untreated
ceramic surface



ceramic surface treated with
120s Ar/O₂⁺
atmospheric pressure plasma



ceramic surface with low roughness

Fig. 4A

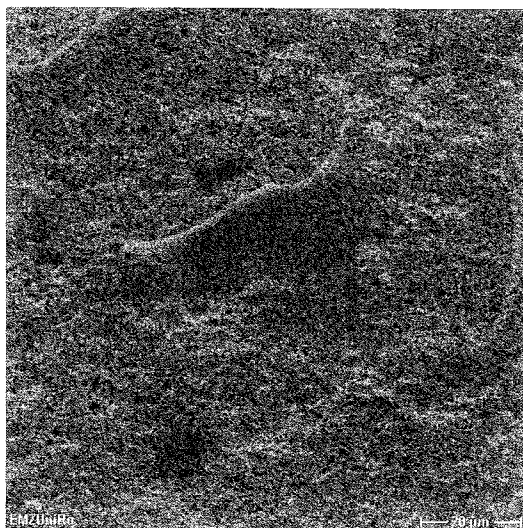
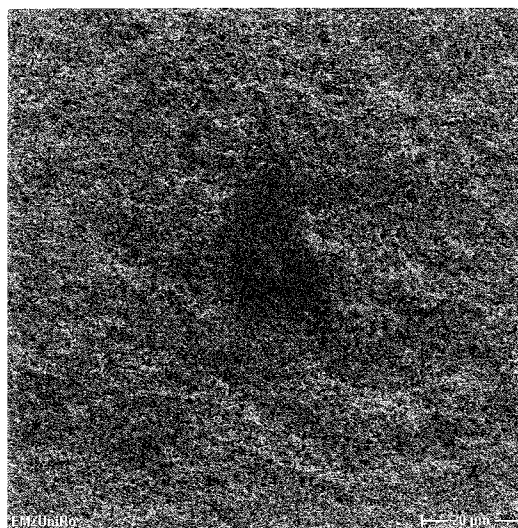


Fig. 4B



ceramic surface with high roughness

Fig. 4C

Fig. 4D

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2012/067286

A. CLASSIFICATION OF SUBJECT MATTER

INV. C04B41/83 A61K6/02 A61L27/34
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C04B A61L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, COMPENDEX, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01/85635 A1 (NKT RES AS [DK]; WINTHER JENSEN BJOERN [DK]) 15 November 2001 (2001-11-15) claims	1-10
Y	CH 702 731 A1 (BIWI SA [CH]) 31 August 2011 (2011-08-31) claims paragraph [0001] paragraph [0057]	1-10
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Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search

29 October 2012

Date of mailing of the international search report

07/11/2012

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2012/067286

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>PULEO D A ET AL: "A technique to immobilize bioactive proteins, including bone morphogenetic protein-4 (BMP-4), on titanium alloy", BIOMATERIALS, ELSEVIER SCIENCE PUBLISHERS BV., BARKING, GB, vol. 23, no. 9, 1 May 2002 (2002-05-01), pages 2079-2087, XP004345254, ISSN: 0142-9612, DOI: 10.1016/S0142-9612(01)00339-8 abstract</p> <p style="text-align: center;">-----</p>	1-10
A	<p>WO 2009/103775 A2 (LENZ SORIN [AT]) 27 August 2009 (2009-08-27) claims page 6, line 32 - line 33</p> <p style="text-align: center;">-----</p>	1-10
A	<p>SIOW K S ET AL: "Plasma methods for the generation of chemically reactive surfaces for biomolecule immobilization and cell colonization - A review", PLASMA PROCESSES AND POLYMERS 20060815 WILEY-VCH VERLAG DE, vol. 3, no. 6-7, 15 August 2006 (2006-08-15), pages 392-418, XP002668952, DOI: DOI:10.1002/PPAP.200600021 cited in the application the whole document</p> <p style="text-align: center;">-----</p>	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/067286

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WO 2009103775	A2	27-08-2009	NONE