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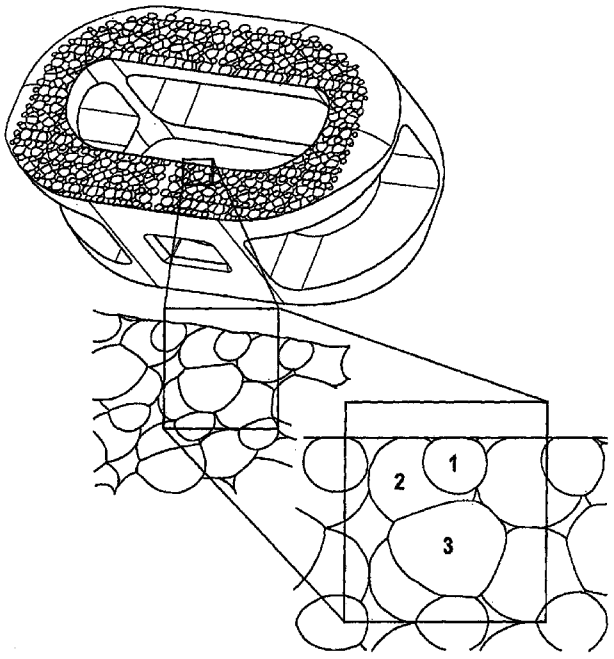

(57) Abstract: An implantable device for treating disc degenerative disease and artliritis of the spine. The implant is sized for placement into an intravertebral disc space. The implant has a body with a predetermined, defined, repeating, three-dimensional pattern at least partially on at least one of its surfaces. The pattern is adapted to create a surface area of bone-contacting features that enhance in-growth and biological attachment to a biocompatible material. Also disclosed are process steps for making the implant.

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MICROSTRUCTURED IMPLANT SURFACES

TECHNICAL FIELD

The present invention relates to microstructured medical implant surfaces, and to processes for producing such surfaces. This invention also relates generally to the treatment of disc degenerative disease or arthritis of the spine and to spinal implants having microstructured surfaces used to treat such conditions.

BACKGROUND OF THE INVENTION

In the simplest terms, the spine is a column made of vertebrae and discs. The vertebrae provide the support and structure of the spine while the spinal discs, located between the vertebrae, act as cushions or "shock absorbers." These discs also contribute to the flexibility and motion of the spinal column. Fig. 1A (described in greater detail below) shows a perspective view of a healthy vertebral column including a disc separating vertebrae.

Over time, the discs may become diseased or infected, develop deformities such as tears or cracks, or simply lose structural integrity, for example discs may bulge or flatten. These impaired discs can affect the anatomical functions of the vertebrae, due to the resultant lack of proper biomechanical support, and are often associated with chronic back pain. Fig. 1B (also described in greater detail below) shows a perspective view of a vertebral column including a damaged disc and vertebrae.

Disc degeneration may occur as part of the normal aging process or as a result of traumatic injury to the soft and flexible disc positioned between the vertebrae. The resulting structural collapse under load may cause, among other things, significant pain and loss of motion. Due to these conditions, other health issues may result.

Where the goal of the treatment of such health issues is to rigidly fix individual spinal vertebra after the surgical removal of damaged or diseased disc tissues, the engagement and subsequent integration of implant surfaces in contact with the vertebral bone is required. Rigid fixation helps to enhance immediate recovery from surgery and helps both in the early stages of healing and over the longer term. Loads through daily activities over the longer term are shared between the implanted device, or implant, and

the resulting osseous (i.e., comprised of, containing, or resembling bone) growth in and around the device.

Some implants are treated using various methods, including coatings, etching processes utilizing chemicals, and acids resulting in roughened or prepared surfaces that enhance bone in-growth. See, for example, U.S. Patents No. 5,876,453, No. 5,258,098, U.S. 6,923,810 to Michelson and U.S. 7,311,734 to Van Hoeck et al., each of which is incorporated by reference herein. The patterns generated in these processes are often intentionally random and irregular. Many acid-etched surfaces on implant devices, for example, are random and irregular due to the application of masking materials in an intentionally random manner. These surfaces are not optimum because they are inconsistent between devices and are difficult to manufacture with precision and repeatability. Patterned surfaces also typically may have only one depth from the original surface and as a result the depth can have too deep a feature that in effect raises stresses between the bone and implants. By using multiple cuts of a predetermined depth and overlapping at a designed interval the overall effect of improved stability is balanced against over stressing the osseos interface.

Because bone tissues are organic and irregular in their growth patterns, the tissues will adhere in an irregular manner regardless of the surface pattern or orientation. This adherence is often sufficient for the initial stabilization, but not necessarily the most efficient way to prevent movement in the critical early healing phases after implantation. Long-term bone in-growth does not necessarily benefit from the irregular patterns, but is not necessarily hindered by it either.

The stimulation of bone growth through specific patterns include textures and roughness in the macro, micron/submicron and nano sized range also has benefit when coupled to this regular repeating surface architecture. While osseous tissues do not form in regular 3 dimensional structures it does follow a well-established pattern for growth which our device stimulates through the multiple surface preparation steps. The combination of stress induced remodeling of a stimulated bone cell in apposition to this prepared surface results in the overall device enhancing and accelerating the fusion of the device and bone structures. See image of bone structure and the Haversian Canals that typical form in the biologic structure noting the regular patterns at the cellular level e.g.,

Paul R. Odgren et al.; "Bone Structure" Encyclopedia of Endocrine Disease, Vol. 1, pp. 392-400 (2004) which is incorporated by reference herein.

Optimizing the pattern of the surface, but intentionally removing materials in patterns and through defined depths of features (e.g., teeth, grooves, sharp edges, ridges, anchoring fins (barbs) and shapes (e.g. U.S. 5,207,709, Picha also incorporated by referenced herein), may improve the biological growth of the tissues. Often this result is achieved with very large surface features machined or molded into implant devices. Larger features have an unintentional and difficult-to-measure side effect of localizing forces and can, over time, result in changing osseous integration. Therefore, the device becomes less stable or, through stress, induces necrosis remodeling. This is a commonly observed result in orthodontic treatment where loading is focused to move teeth in a patient's mouth to reposition dentition in a more effective location for mastication and esthetics. Although it is understood that loading can move and reshape bones, each patient and even each area of the skeletal structure is variable and therefore ideal large features often do not work in all applications and all patients. Other factors such as overall health, subsequent health conditions, degenerative conditions, and traumatic events add to this dynamic environment.

Other problems confront surgeons. For example, some surfaces are random and not well suited to the location of implantation, direction of loading, and forces acting on the implants due to daily activities. The results may include poor support of the spinal column or traumatic surgeries. These, in turn, may result in complications and increase patient traumatic suffering. Orientation of the surface patterns in parallel to the original surfaces is also enhanced by the depth of surface cuts and planes that can be designed to function more effectively in resisting directional loading and to be an advantage of a designed surface having three components, namely the width, length and also depth of the designed patterns.

To overcome the shortcomings of conventional spinal implants, a new spinal implant having an improved surface treatment is provided. An object of the present invention is to provide an implant surface having a pattern that is substantially uniform over the area of the implant that is intended to bond to the bone in which the implant is placed. A related object is to provide an improved surgically implantable device having

on its surface a substantially uniform and bioactive micromorphology. It is another object of the invention to provide a process or processes for manufacturing such improved implant devices. A more specific object is to provide an improved process that yields a substantially uniform surface topography designed intentionally to enhance healing and long term function of surgically implantable devices.

It is to be understood that the present invention while directed primarily to spinal implants is not limited thereto. The advantageous implant surface created in practice of this invention obtains a surprising and unexpected osteointegration in the context of spinal repair that can be applicable in other situations. It is believed that the present invention can be applied in many medical circumstances where bone in-growth to the surface of a prosthetic device is important to the success of the cosmetic or therapeutic procedure. For example, lower body bone repair, e.g., foot/ankle, and dental prosthetic procedures utilizing prosthetic devices where bone in-growth is required are likely to have their success significantly improved by the use of devices having surfaces produced according to this invention.

SUMMARY OF THE INVENTION

The present invention provides an implantable device comprising a body, the body having a surface and a plurality of connections sized, in one embodiment, for placement into an intravertebral disc space. The surface has a defined, repeating, three-dimensional pattern that provides a surface area of bone-contacting features that allow for and encourage in-growth of bone and proteinaceous materials and biological attachment to a biocompatible material i.e., integration. The three dimensional surface morphology incorporates overlapping patterns of features in two dimensions as well as different and independent thereof dimensional depths for each of the features.

Another aspect of the invention is a method of making an implant device, the implant device comprising an implant body, the body defining a working surface, the surface having a first defined pattern on the surface; adding a second defined pattern on the surface, the second defined pattern overlapping the first defined pattern; and including at least one other defined pattern on the surface that overlaps with the first and second defined patterns.

It is to be understood that both the foregoing general description and the following detailed description are exemplary, but are not restrictive, of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is best understood from the following detailed description when read in connection with the accompanying drawings and the attached claims. It is emphasized that, according to common practice, the various features of the drawings are not to scale. On the contrary, the dimensions of the various features are arbitrarily expanded or reduced for clarity. Included in the drawings are the following figures:

Fig. 1A shows a perspective view of a healthy vertebral column including a disc separating vertebrae;

Fig. 1B shows a perspective view of a vertebral column including a damaged disc and vertebrae;

Fig. 2 shows a perspective view of a prior art spinal implant;

Fig. 3A shows a perspective view of the spinal implant of the present invention;

Fig. 3B shows a partial perspective view highlighting a portion of the implant illustrated in Fig. 3A;

Fig. 4A shows a partial top view of a surface of the implant of the present invention following a first exemplary processing step;

Fig. 4B shows a partial top view of the surface of the implant of the present invention shown in Fig. 4A, following a second exemplary processing step;

Fig. 4C shows a partial top view of the surface of the implant of the present invention shown in Fig. 4B, following a third exemplary processing step; and

Fig. 4D shows a top view of the completed surface of the implant of the present invention following the processing steps shown in Figs. 4A, 4B, and 4C.

FIGS. 5A, 5B, and 5C show confocal laser microscopy images and average-roughness (S_a) values of PEEK (A), sTiAIV (B), and rTiAIV (C) surfaces of 644 x 644 μm^2 field.

FIGS. 6A, 6B, 6C, 6D, 6E, and 6F show SEM images of PEEK (A, B), sTiAIV (C, D), and rTiAIV (E, F) surfaces at low and high magnifications.

FIG. 7A Shows the three features; Macro, Micron/Submicron and Nano size.

FIG. 7B Shows the size range and roughness of the Macro feature.

FIG. 7C Shows the size range and roughness of the Micron/Submicron features.

FIG. 7D Shows the size range and roughness of the Nano feature.

FIGS. 7A-7D show relative size limitations and surface roughness features of this invention.

FIG. 8 shows an exemplary dimple pattern surface of this invention in macroscopic and microscopic detail. The patterns of dimples 1, 2, 3 are overlapping, but they are sized and aligned so as not to either remove the previous dimple. In FIG. 8 the depth is greatest for 1 and ascends till step 3 with the sizes of the cuts increasing from 1 to 3.

FIG. 9 is a schematic representation of human osteoblast-like MG63 cell cultures in accordance with an embodiment of the present invention.

FIGS. 10A, 10B, 10C, and 10 D are tables showing values obtained from human MG63 osteoblast-like cells harvested 24 hours after confluence on TCPS.

FIGS. 11A, 11B, 11C, and 11D are tables showing values obtained from human MG63 osteoblast-like cells harvested 24 hours after confluence on TCPS.

FIGS. 12A, 12B, 12C, 12D, 12E, 12F, 12G, and 12H are tables showing results from human MG63 osteoblast-like cells harvested 12 hours after confluence on TCPS.

DETAILED DESCRIPTION OF THE INVENTION

Referring now to the drawings, in which like reference numbers refer to like elements throughout the various figures that comprise the drawings, Fig. 1A shows a spinal column 100 including an upper vertebra 102 and a lower vertebra 103 separated by a healthy, flexible disc 104a. Fig. 1B shows the spinal column 100 with the upper vertebra 102 and the lower vertebra 103 separated by a damaged or collapsed disc 104b. The damaged disc 104b typically requires surgical intervention to attain fusion and stabilization for complete healing and the relief of pain. A device according to this invention, e.g., a spinal implant, is used to replace the damaged disc 104b and provides strong initial stability, rapid healing, and bone repair.

As illustrated in Fig. 2, certain embodiments of the present invention include an interbody spinal implant 1 that serves as a spacer between adjacent vertebrae. The implant 1 may be comprised of titanium, a titanium alloy, organic polymers such as polyaryletheretherketone ("PEEK") materials, ceramics, and other suitable materials known to people of skill in the art. The implant 1 comprises an implant body 5 with a top surface 10, a bottom surface 20, opposing lateral sides 30, and opposing anterior 40 and posterior 50 portions. The implant 1 has a sharp edge 8 where the anterior portion 40 meets the top surface 10 and where the anterior portion 40 meets the bottom surface 20. A delivery device (not shown) can engage opening 90 in the anterior portion 40 of the implant 1, allowing the user to manipulate the implant 1 during placement between vertebrae.

The implant 1 is substantially hollow and has a generally oval-shaped transverse cross-sectional area with smooth and/or rounded lateral sides and rounded posterior-lateral corners. The implant 1 includes at least one aperture 60 that extends the entire height of the implant body. The implant 1 may further include at least one aperture 70 that extends the entire transverse length of the implant body. These transverse apertures 70 may provide improved visibility of the implant 1 during surgical procedures to ensure proper implant seating and placement, and may also improve post-operative assessment of implant fusion. Still further, the substantially hollow area may be filled with cancellous autograft bone, allograft bone, demineralized bone matrix (DBM), porous synthetic bone graft substitute, bone morphogenic protein (BMP), or combinations thereof, to facilitate the formation of a solid fusion column within the patient's spine.

As illustrated in Figs. 3A and 3B, the implant 1 further includes a designed surface topography 80. The designed surface topography 80 is provided on at least a portion of the top surface 10, the bottom surface 20, or both the top and bottom surfaces 10, 20 of the implant 1 for gripping adjacent bone and inhibiting migration of the implant. Preferably, each surface 10 and 20 has a designed surface topography 80 that promotes anchoring and healing of spinal tissues.

It is generally believed that the three-dimensional surface of the implant 1 determines its ultimate ability to integrate into the surrounding living bone. Without being limited by theory, it is hypothesized that the cumulative effects of at least implant

composition, implant surface energy, and implant surface topography play a major role in the biological response to, and osteointegration of, the implant 1.

The addition of macro, micron/submicron and nano sized features in the ranges as stated in the table below stimulate the growth of the bone cellular structures by working in concert with well understood bone modeling and structures. The overall 3 dimensional shape of bone is not of a repeating structure but at a cellular level as in the Haversian Canal the structure is repeating and regular. By stimulating the biological behavior of the bone cells the resulting stimulation works in concert with the other structural features of the invention and balances the performance of the implant as a fusion device with sufficient resistance to expulsion and mobility to succeed in the initial stabilization of the device and the long term incorporation of rigid fusion of the vertebrae.

Surface Feature size and Roughness

Macro		Micron/Submicron		Nano	
Size (Rz)	Roughness (Ra)	Size (Rz)	Roughness (Ra)	Size (Rz)	Roughness (Ra)
50µm - 200µm	10µm - 30µm	500nm - 20µm	5µm - 10µm	200nm - 500nm	.5µm - 5µm

These features in the ranges of peak size or crest to crest of the indentation (Rz) and with an average surface roughness (Ra) are applied on top of the three machined or etched expulsion features and cover the entirety of the implant and are also on the surfaces of the implant in areas where there is not an anti-expulsion surface pattern. The nano sized features unlike many other published structures are indented into the surface or subtracted from the base material through post processing etching and blasting methods and therefore have an inherent structural rigidity that is not found in protruding tube features in the nano size range.

"Osteointegration" as that term is used here is intended to mean the formation of a direct structural and functional interface between an artificial implant, and living boned. In a narrower sense, osteointegration occurs without the presence of soft tissue between bone and implant.

Thus, implant fixation may be, at least in part, dependant on the attachment and proliferation of osteoblasts, and like functioning, cells upon the implant surface. Still

further, it appears that these cells attach more readily to relatively rough surfaces rather than smooth surfaces. In this manner, a surface may be bioactive due to its ability to facilitate cellular attachment and osteointegration. Without being limited by theory, it is believed that the designed surface topography and predefined depths of these features 80 may better promote the osteointegration of the implant 1. The designed surface topography 80 may also better grip the vertebral endplate surface(s) and inhibit implant migration upon placement and seating. This is accomplished through the designed patterns of the features including the depths of the overlapping patterns.

Thus, the present invention provides the implant 1 having an implant body 5 that defines a designed surface topography 80 that is both three dimensional and intentionally patterned. The designed surface topography 80 is produced in multiple steps using tooling of a specified shape and size. The designed surface topography 80 is adapted to create a large surface area of bone-contacting features that allow for in-growth and biological attachment to a biocompatible material.

The designed surface topography 80 of an implant 1 of this invention has specific patterns. By overlapping these patterns, the designed surface topography 80 may be used as an integration surface with features of a desirable size for bone growth (specifically implant in-growth) and attachment and to aid in resisting forces that act on the implant 1, thereby improving stability and overall success of the procedure. The designed surface topography 80 with a defined pattern of the implant 1 facilitates the installation of the implant 1 and enhances the initial, intermediate, and long-term stability of the implant 1.

The designed surface topography 80 is created using predictable and repeatable process steps, such as mechanical or chemical machining, photo etching or adaptations of laser or plasma welding technologies. These steps allow for variations of the surface patterns on individual implant working surface so that areas that may benefit from more or less aggressive features may be formed. The three dimensional patterns can also be varied is ways that can be used to fine tune various areas of the implant bodies initial fixation due to contact with the vertebral body and it's relative construction. More specifically, the use of microscopic mechanical or chemical machining, photo etching or adaptations of laser or plasma welding technologies generating repeating patterns in multiple overlapping steps onto a surface that is refined with e.g., a post machining and

abrasive media blasting step, or acid etching, results in a macro and micro designed surface topography 80 that effectively integrates with bone. In addition, the designed surface topography 80 may be oriented to resist biological loading better than randomly generated surfaces.

By analogy, treads on automobile tires are designed with specific functions in mind: grip in the forward direction, for example, and stability in the lateral direction. Similarly, the designed selected, planned or strategically chosen surface topography 80 of the present invention can be predetermined with specific functions in mind. (By "predetermined" is meant determined beforehand, so that the predetermined pattern is determined, i.e., chosen, selected or at least known or in mind, before processing begins and in view of the post-implant medical environment). The designed surface topography 80 on the top surface 10 in the anterior portion 40 may have larger and sharper features to resist expulsion of the implant 1 from between the vertebrae, for example, while the designed surface topography 80 on the top surface 10 in the posterior portion 50 may have smaller and less sharp features to facilitate placement of the implant 1. This flexibility gives the designer options to achieve desired performance characteristics and the designer can both optimize and enhance the performance of the implant 1 having the designed surface topography 80. Preferably, the implant 1 does not have any unintentional sharp edges or protrusions (excepting sharp edges 8 which are intentionally provided to permit implant 1 to resist expulsion from between adjacent vertebra). These sharp edges or protrusions sometimes result in focal points for loading and the resulting loss of osseous tissues through stress-induced bone loss. This is also considered in concert with the structural properties of the vertebral body, which is commonly stiffer on the outer edges and has greater mobility towards their center surfaces. The implant surface that has synthetic and or biologically derived materials applied to it allows for "seeding" in specific locations of these materials acting in concert with the microscopic surface enhancements generated in the production process. With or without the addition of growth-enhancing materials and surface geometry, the designed surface topography 80 has features in a defined size range that are beneficial to the biological growth and remodeling of bone tissues subjected to loading in several directions.

The designed surface topography 80 of the implant 1 is the connection point for the load-bearing or working surface of the implant 1 and the live osseous tissue of the vertebrae. The designed surface topography 80 allows for initial stabilization and long-term bone in-growth and fusion. Larger surface areas and a smooth and contoured surface provide more assured and effective initial, intermediate, and long-term outcomes and overall benefit to a patient.

Using micro surfaces created through subtractive chemical or mechanical processes is an achievable and commercially viable way to increase the surface area for dissipating variable loads and compensating for variable bone conditions. Smaller features that allow for dissipated forces but having a regulated, designed pattern are beneficial in treating the largest possible number of patients having the largest number of variables.

Through careful design of readily available micro machine tools, photo etching, and other processes of microscopic machining and advanced manufacturing equipment and adaptation of these processes using repeating and multiple overlapping patterns of varying depths, surfaces that have the same roughened contours as chemically etched surfaces may be achieved. The patterns, depth diameters, and other manufacturing process settings generate a designed surface topography 80 having three-dimensional contour, directional stability, and long-term success. The addition of general acid or abrasive media post machining preparation provides the benefits of refining the surface, removing sharp edges resulting from the machining, and adding a micro texture to the implant integration surface.

Exemplary embodiments of the implant body comprise many various bodies of various sizes and biocompatible materials that have surface enhancements consistent with the designed surface topography 80 of machined and acid etching refined surfaces. The designed surface topography 80 can be formed in multiple steps using very small tooling often referred to as micro drills or milling cutters in high speed, highly precise, milling equipment. These practices are contrary to common efforts to remove large amounts of material as quickly as possible. Optimization of the surface geometry and the ability to define repeating patterns to predefined depths is beneficial to the overall product design can be achieved using these processes and others.

The following exemplary process steps are included to more clearly demonstrate the overall nature of the invention. These steps are exemplary, not restrictive, of the invention. The sequential process steps shown in Figs. 4A, 4B, and 4C illustrate multiple layers and steps of implant machining.

As shown in Fig. 4A, the first process step creates a first feature 82 of the designed surface topography 80 on the top surface 10 of the implant 1. The first feature 82 is typically the deepest feature of the designed surface topography 80 and may be, for example, 0.021 inches deep (or more) into the surface of the implant 1 (along the Z axis as illustrated). A wide variety of processes can be applied to create the first feature 82. As illustrated, the first feature is a spherical indent which might be created, for example, by the use of a ball-shaped tool (e.g., by "peening" or drilling). In processing circumstances where surface material is displaced to create surface topography it will be understood that subsequent processing or finishing steps e.g., polishing, may be employed to remove incidentally-created surface artifacts which are not part of the feature.

The designed surface topography 80 of the implant 1 is produced by overlapping several features. In Fig. 4B, the second process step creates a second feature 84 of the designed surface topography 80 of the implant 1 but up to the depth of the first feature. The second feature 84 is typically the second deepest feature of the designed surface topography 80 and may be, for example, 0.014 inches deep into the surface of the implant 1. A wide variety of processes can be applied to create the second feature 84. The depth and X-Y placement of the second feature 84 are selected so that the second feature 84 does not directly overlap and wipe out the first feature 82 (to highlight the second feature 84 and for purposes of clarity the first feature 82 is not shown in Fig. 4B although the first feature 82 exists in combination with the second feature 84). The depth variations and alignment to the expected load direction will have the same net effect as a single feature of the same depth, but in other lower loaded directions will minimize focused loading and reduce stresses that the bone is subjected to when lower loading is applied. As with the first feature 82 incidentally-created process artifacts e.g., burrs, splays, may need to be removed using well known techniques.

As shown in Fig. 4C, the third process step creates a third feature 86 of the designed surface topography 80 of the implant 1. The third feature 86 is typically the shallowest feature of the designed surface topography 80 and may be, for example, 0.007 inches deep into the surface of implant 1 but less than the depth of the second feature 84. A wide variety of processes can be applied to create the third feature 86. The depth and X-Y placement of the third feature 86 are selected so that the third feature 86 does not directly overlap and wipe out the first feature 82 or the second feature 84 (to highlight the third feature 86 and for purposes of clarity the first feature 82 and the second feature 84 are not shown in Fig. 4C although the first feature 82 and the second feature 84 exist in combination with the third feature 86). Note that the right-most column of the third feature 86 as illustrated in Fig. 4C appears smaller than the remainder of the third feature 86 only because the third feature 86 extends beyond the top surface 10 and onto the lateral side 30 a short distance.

Of course, processes with more or fewer than three steps can be used to create any predetermined pattern for the designed surface topography 80. And each process step can create a feature that differs (in type, size, shape, location, and other characteristics) from the features illustrated in Figs. 4A, 4B, and 4C. Figs. 4A, 4B, and 4C depict exemplary process steps with different surfaces. As completed for the example illustrated, the designed surface topography 80 following the multi-step sequential application of process steps (shown as bracket 88 and indicating the completed workpiece or working surface) and final working surface of implant body 5 is shown in Fig. 4D. The implant 1 illustrated in Fig. 4D combines machined and acid etched micro surfaces that behave in a similar manner with regard to the bone tissues, but add directional stability by having an organized pattern that resists loading and potential movement of the implant 1.

The designed surface topography 80 of the implant 1 is produced by overlapping several features. This results in a large surface area of defined geometric shapes and patterns. Preferably, the process steps include repeating shapes between the machining steps to produce a large surface area having a defined pattern. The designed surface topography 80 may also be refined using mechanical, focused energy or chemical processes to improve the implant surface.

Thus, the designed surface topography 80 may be obtained through a variety of techniques including, without limitation, chemical or acid etching, shot peening, plasma etching, laser etching, or abrasive blasting, such as sand or grit blasting. In one process step embodiment of the present invention, a roughened surface topography is obtained via the repetitive masking and chemical or electrochemical milling processes described in U.S. Patents No. 5,258,098; No. 5,507,815; No. 5,922,029; and No. 6,193,762, each incorporated herein by reference. By way of example, an etchant mixture of nitric acid and hydrofluoric acid (HF) may be repeatedly applied to a titanium surface to produce an average etch depth of about 0.021 inches. Interbody spinal implants 1 may be comprised, in accordance with preferred embodiments of the present invention, of titanium or a titanium alloy having an average surface roughness of about 100 μm on the top surface 10 and on the bottom surface 20. Surface roughness may be measured using a laser profilometer or other standard instrumentation.

The implant surface is produced using defined and adapted tooling that, when patterns of these features are overlapped in a predetermined manner, result in an improved surface capable of sustaining osseous in-growth under loading. Various chemicals, such as acids, may be used to refine the contours of the implant surface. The result of such refinement is a relatively smooth surface free from manufacturing debris and well adapted to biological behavior of bone tissues.

Due to their small size and limited operational access, implants 1 of the exemplary type are typically difficult to manipulate and precisely place without instruments. The body of the implant typically includes at least three, and sometimes more than three, instrument connections (such as the opening 90) that can be threaded, force fit, or snap fit together to rigidly connect the implant 1 and withstand placement in the vertebrae. The force fit of the implant 1 into the intravertebral space creates initial stability of the device and incorporates the bone tissues into the surface of the implant 1.

EXAMPLES

Background

Titanium implants with physical-chemical modifications such as micron or submicron scale topographic features have been shown to increase osteoblast differentiation and

local factor production *in vivo* and to increase peri-implant bone formation and decrease healing time *in vivo*. Polyetheretherketone (PEEK) is used as a cage or spacer in vertebral interbody fusion to maintain spinal alignment and segmental stability while facilitating bony fusion. The aim of this analysis was to elucidate whether common intervertebral materials such as PEEK and titanium alloy (Ti6AI4V) induce osteoblast maturation and generate an osteogenic environment.

Methods

The methods employed herein are shown below.

Human osteoblast-like MG63 cells were cultured on tissue culture polystyrene (TCPS), PEEK, or smooth [sTi6AI4V, Sa>90nm] and rough [rTi6AI4V, Sa=1.81μm] Ti6AI4V surfaces as shown in FIG. 9. Gene expression was measured by qPCR. Osteoblast maturation was assessed by analysis of cell number, alkaline phosphatase activity (ALP), and secreted osteocalcin, osteoprotegerin, TGF-ß1, BMP2, BMP4, and BMP7. Data are mean±SEM (n=6/condition), analyzed by ANOVA with Bonferroni's modification of Student's t-test.

Results

FIGS. 5A, 5B, and 5C. Confocal laser microscopy images and average-roughness (S_a) values of PEEK (A), sTiAIV (B), and rTiAIV (C) surfaces of 644 x 644 μm^2 field.

FIGS. 6A, 6B, 6C, 6D, 6E, and 6F. SEM images of PEEK (A, B), sTiAIV (C, D), and rTiAIV (E, F) surfaces at low and high magnifications.

Human MG63 osteoblast-like cells were harvested 24 hours after confluence on TCPS. Cell number, alkaline phosphatase specific activity in cell lysates and levels of osteocalcin, osteoprotegerin, active TGF-ß1, latent TGF-ß1, BMP2 and BMP4 in the conditioned media were measured. *p<0.05, v. TCPS; #p<0.05, v. PEEK; $p<0.05, v. sTiAIV. The values obtained are shown in FIGS. 10A-D and FIGS. 11-A-D.

Human MG63 osteoblast-like cells were harvested 12 hours after confluence on TCPS. Levels of mRNA for integrins alpha 1 (ITGA1), alpha 2 (ITGA2), alpha v (ITGAV), and beta 1 (ITGB1), BMP2 (A) and BMP4, and BMP inhibitors noggin (NOG) and gremlin 1 (GREM1) were measured by real-time qPCR and normalized to GAPDH. *p<0.05, v. TCPS; #p<0.05, v. PEEK; $p<0.05, v. sTiAlV. Results are shown in FIGS. 12A-H .

Discussion

The results indicate that osteoblasts on Ti6Al4V surfaces present a more mature phenotype than osteoblasts grown on PEEK. Cells on Ti6Al4V, but not PEEK, produce an osteogenic environment. Osteoblasts cultured on Ti6Al4V produce and regulate BMP pathway molecules, increasing BMP2, BMP4, BMP7, and physiologic BMP inhibitors. One reason for the differential response of osteoblasts to PEEK and TiALV may result from differences in integrin expression downstream signaling by these receptors. Taken together, surface properties, including the composition of the bulk material, are important in directing cell response to implant materials, ultimately affecting implant success. The results demonstrate that Ti6Al4V surfaces positively modulate osteoblast maturation and regulate BMP signaling.

The instrumentation and installation practices of this invention are used in not only spinal surgery, but also in common orthopedic treatment of many of the bones and joints in the body. Common hip and knee implants often use a force fit or interference fit to initially stabilize the implants and promote long-term success. These instruments and the connection to the implants are correspondingly durable and robust enough to withstand loading, impacts, and forces resulting from the procedures.

Although illustrated and described above with reference to certain specific embodiments and examples, the present invention is nevertheless not intended to be limited to the details shown. Rather, various modifications may be made in the details within the scope and range of equivalents of the claims and without departing from the spirit of the invention. It is expressly intended, for example, that all ranges broadly recited in this document include within their scope all narrower ranges which fall within the broader ranges.

What is Claimed is:

1. An implantable device comprising:

a body, the body having a surface and being sized for placement into an intravertebral disc space, the surface having a defined, repeating, three-dimensional pattern, the three-dimensional pattern resulting from the application to the surface of first and second two-dimensional surface patterns; each said first and second patterns having a depth dimension, the first said pattern depth dimension being greater than the second depth dimension to create a surface area of bone-contacting features that allow for in-growth and biological attachment to a biocompatible material.

2. An implantable device according to claim 1 wherein the first and second two-dimensional patterns are non-overlapping.

3. An implantable device according to claim 1 wherein the surface is created by application to the surface of,

first, second, and third two dimensional surface patterns, each said first, second and third surface pattern also having a depth dimension, the depth dimension of the first pattern being greater than the second depth dimension and the second depth dimension being greater than the depth dimension.

4. An implantable device according to claim 3 wherein the first, second, and third two-dimensional patterns are non-overlapping.

5. The implantable device of claim 1 wherein the surface comprises multiple, two-dimensional overlapping patterns of varying depths and predefined orientation to have higher load resistance to a specific load direction without overloading bone tissues.

6. A method of making an implant device comprising:

providing an implant having a surface;

creating a first defined pattern on the surface;

adding a second defined pattern on the surface, the second defined pattern overlapping the first defined pattern; and

including at least one other defined pattern on the surface that overlaps with the first and second defined patterns.

7. An implantable prosthetic device adapted to promote osteointegration, the device comprising:

a body, the body having a surface, the surface having a defined three-dimensional pattern, the three-dimensional pattern resulting from the application to the surface of first and second two-dimensional surface patterns; each said first and second patterns having a depth dimension, the first said pattern depth dimension being greater than the second depth dimension to create a surface area of bone-contacting features that allow for in-growth and biological attachment to a biocompatible material.

8. A device according to claim 7 wherein the two-dimensional surface patterns are non-overlapping.

9. A device according to claim 7 in which the surface has first, second, and third two-dimensional patterns.

10. A device according to claim 9 wherein the first, second, and third two-dimensional patterns are non-overlapping.

AMENDED CLAIMS
received by the International Bureau on 28 February 2013 (28.02.2013)

1. An implantable device comprising:

a body being sized for placement into an intravertebral disc space and having a top surface, a bottom surface, opposing lateral sides, opposing anterior and posterior portions, a substantially hollow center, and a single vertical aperture extending from the top surface to the bottom surface,

the top surface, the bottom surface, or both surfaces having a defined, repeating, three-dimensional pattern, the three-dimensional pattern comprising first and second surface patterns without sharp protrusions; the first surface pattern including a plurality of dimples having a first depth dimension and the second surface pattern including a plurality of dimples having a second depth dimension, the first depth dimension being greater than the second depth dimension to create a designed surface topography of bone-contacting features that allow for in-growth and biological attachment to adjacent bone.

2. The implantable device according to claim 1 wherein a portion of the first surface pattern does not overlap the second surface pattern.

3. The implantable device according to claim 1 further comprising:

a third surface pattern, the third surface pattern comprising a plurality of dimples having a third depth dimension, the second depth dimension being greater than the third depth dimension.

4. The implantable device according to claim 3 wherein a portion of the first surface pattern does not overlap the second surface pattern, and a portion of the second surface does not overlap the third surface pattern.

5. The implantable device of claim 1 wherein the three-dimensional pattern comprises at least three partially overlapping patterns of varying depths and predefined orientation to have higher load resistance to a specific load direction without overloading bone tissues.

6. A method of making an implant device comprising a body being sized for placement into an intravertebral disc space and having a top surface, a bottom surface, opposing lateral sides, opposing anterior and posterior portions, a substantially hollow center, and a single

AMENDED SHEET (ARTICLE 19)

vertical aperture extending from the top surface to the bottom surface, the method comprising:

creating a first defined pattern having a plurality of dimples on the top surface, the bottom surface, or both surfaces;

adding a second defined pattern having a plurality of dimples on the top surface, the bottom surface, or both surfaces, the second defined pattern partially overlapping the first defined pattern; and

including at least one other defined pattern on the top surface, the bottom surface, or both surfaces that partially overlaps with the first and second defined patterns.

7. An implantable prosthetic device adapted to promote osteointegration, the device comprising:

a body having a top surface, a bottom surface, opposing lateral sides, opposing anterior and posterior portions, a substantially hollow center, and a single vertical aperture extending from the top surface to the bottom surface,

the top surface, the bottom surface, or both surfaces having a defined three-dimensional pattern, the three-dimensional pattern comprising first and second surface patterns without sharp protrusions; the first surface pattern including a plurality of dimples having a first depth dimension and the second surface pattern including a plurality of dimples having a second depth dimension, the first depth dimension being greater than the second depth dimension to create a designed surface topography of bone-contacting features that allow for in-growth and biological attachment to a biocompatible material.

8. The device according to claim 7 wherein a portion the first surface pattern does not overlap the second surface pattern.

9. The device according to claim 7 further comprising a third surface pattern.

10. The device according to claim 9 wherein a portion of the first surface pattern does not overlap the second surface pattern, and a portion of the second surface pattern does not overlap the third surface pattern.

11. The device according to claim 9, wherein the third surface pattern has a third depth dimension, the second depth dimension being greater than the third depth dimension.

AMENDED SHEET (ARTICLE 19)

12. The device according to claim 7 wherein the first surface pattern partially overlaps the second surface pattern.

13. The device according to claim 7 wherein the second surface pattern partially overlaps the third surface pattern.

14. The implantable device according to claim 1 wherein the first surface pattern partially overlaps the second surface pattern.

15. The implantable device according to claim 1 wherein the second surface pattern does not directly overlap the first surface pattern.

16. The implantable device according to claim 1 wherein the plurality of dimples for the first surface pattern and the second surface pattern comprise semi-spheres.

17. The implantable device according to claim 1 wherein the body further comprises a sharp edge where the anterior portion meets the top surface, where the anterior portion meets the bottom surface, or at both locations.

18. The implantable device according to claim 1 wherein the first surface pattern comprises macro sized features and the second surface pattern comprises micro sized features.

19. The implantable device according to claim 1 wherein the three-dimensional pattern comprises macro sized, micro sized, and nano sized features.

20. The implantable device according to claim 1 wherein the three-dimensional pattern comprises:

a macro size Rz of 50 μm to 200 μm and a roughness Ra of 10 μm to 30 μm;

a micro size Rz of 500 nm to 20 μm and a roughness Ra of 5 μm to 10 μm; and

a nano size Rz of 200 nm to 500 nm and a roughness Ra of 0.5 μm to 5 μm.

AMENDED SHEET (ARTICLE 19)

Fig. 1A

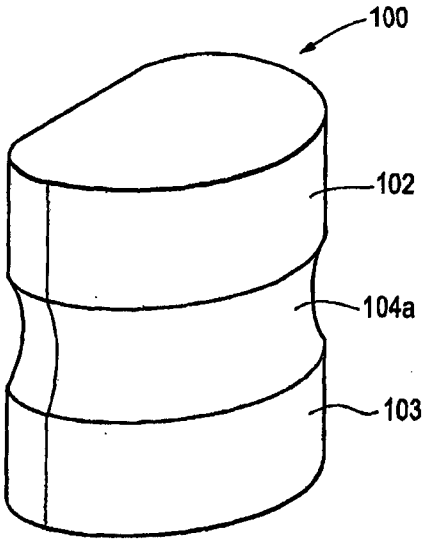


Fig. 1B

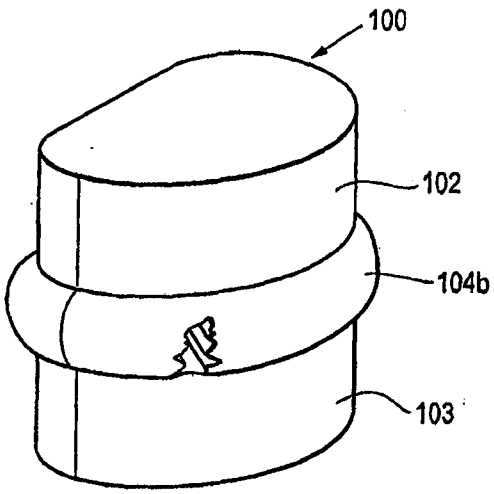


Fig. 2

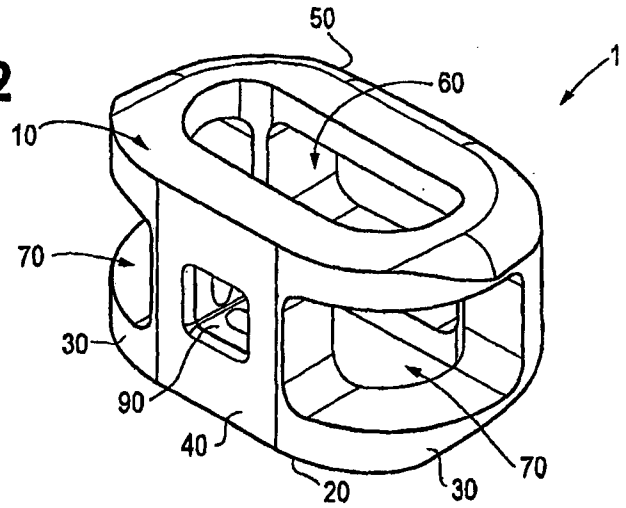


Fig. 3A

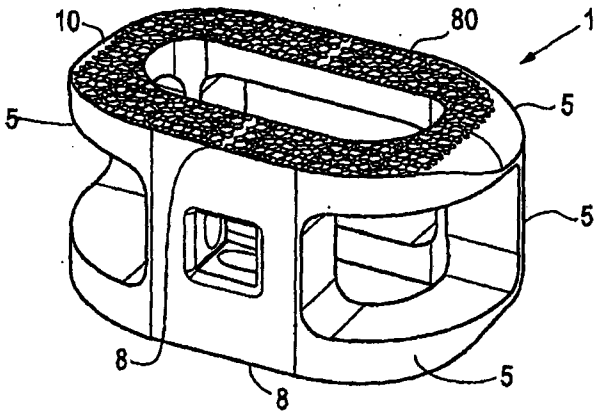


Fig. 3B

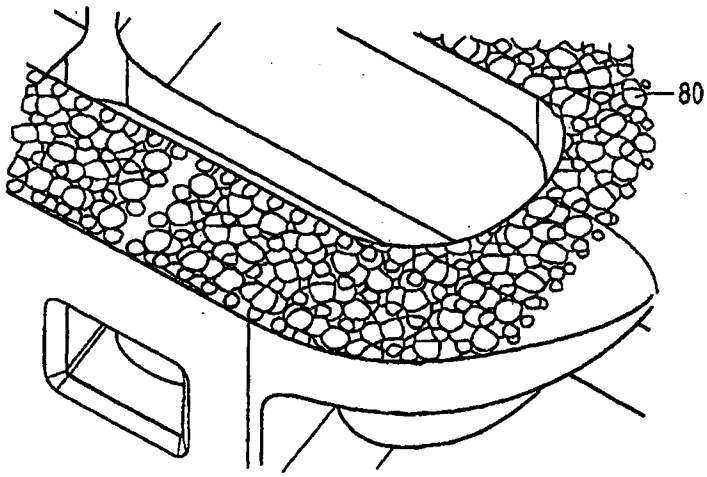


Fig. 4A

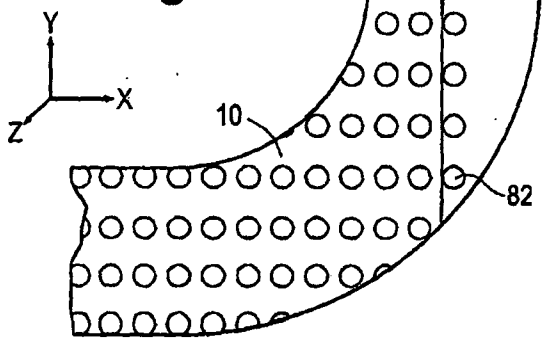


Fig. 4B

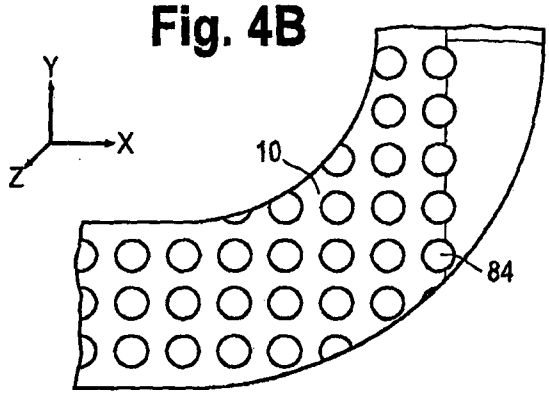


Fig. 4C

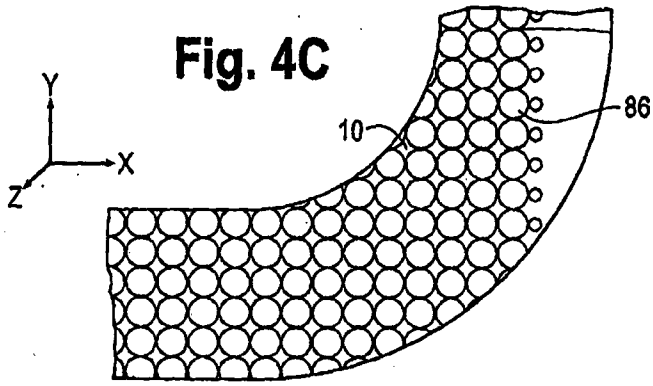
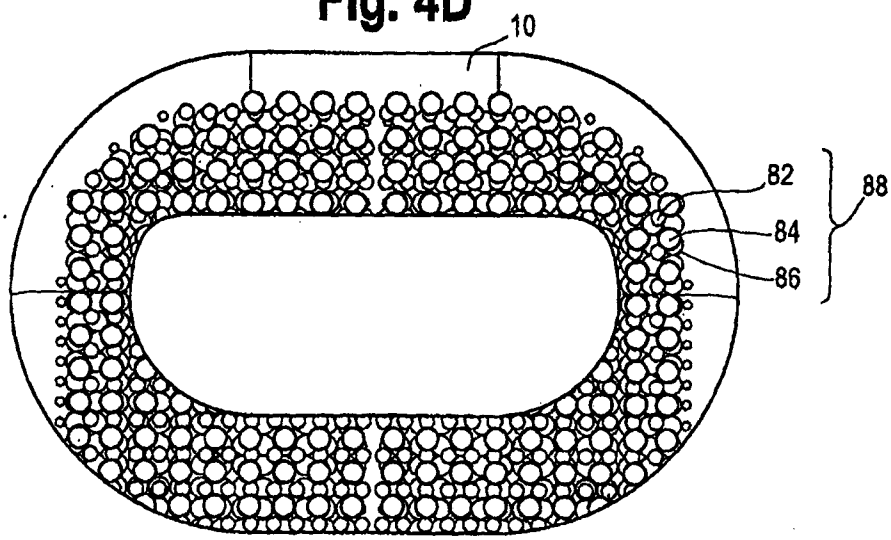


Fig. 4D



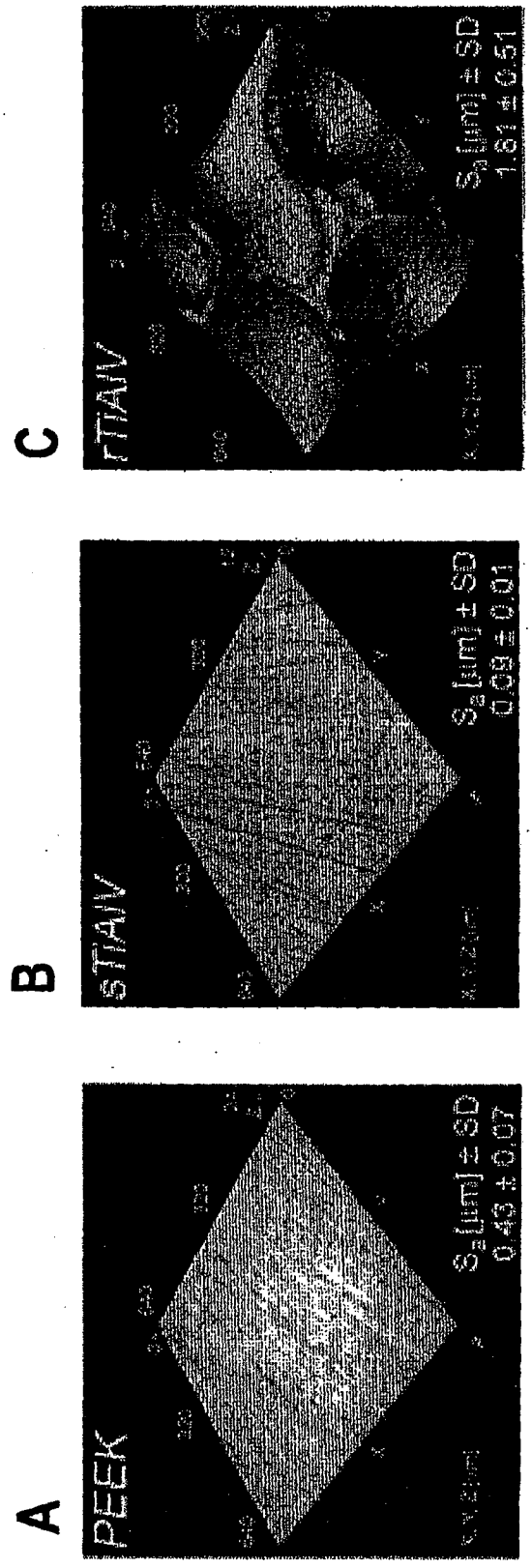


Fig. 5

Confocal laser mircoscopy images and average-roughness (S_a) values of PEEK (A), sTiAlV (B), and rTiAlV (C) surfaces. of 644 x 644 μm^2 field,

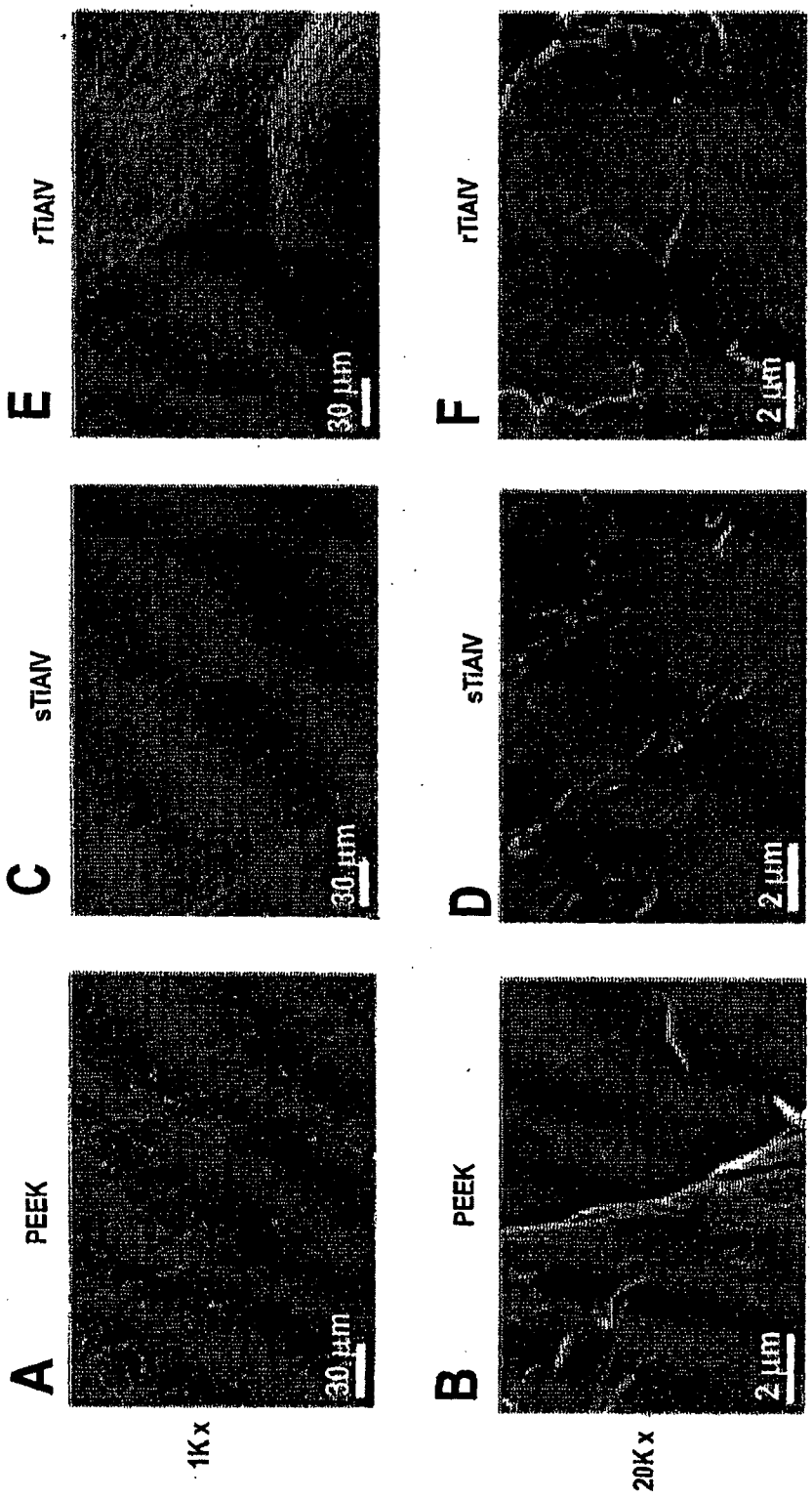
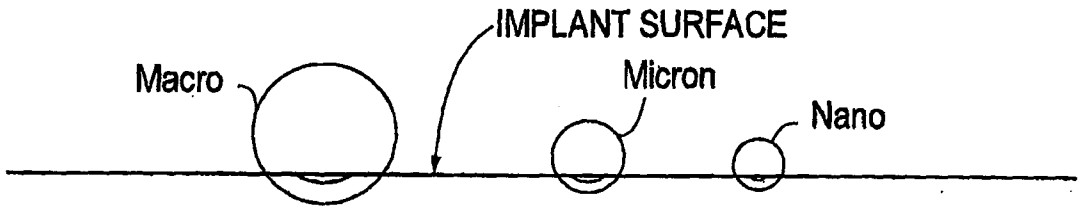


Fig. 6

SEM images of PEEK (A, B), sTiAlV (C, D), and rTiAlV (E, F) surfaces at low and high magnifications.

Fig. 7A



DETAIL Ma
SCALE 40 : 1

Fig. 7B

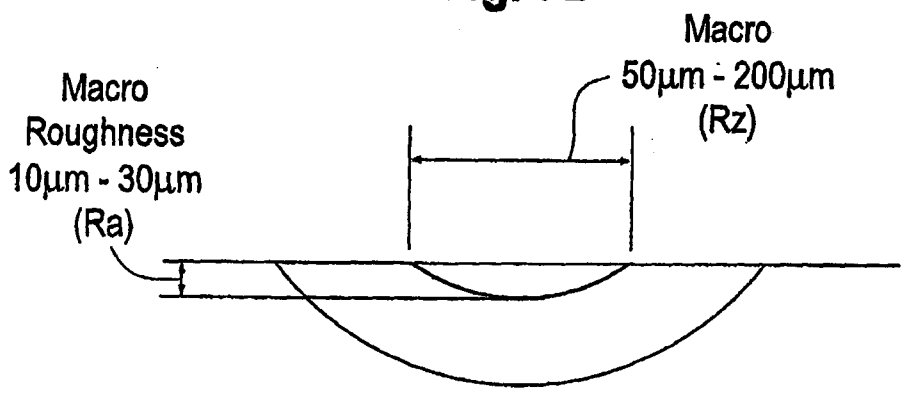


Fig. 7C

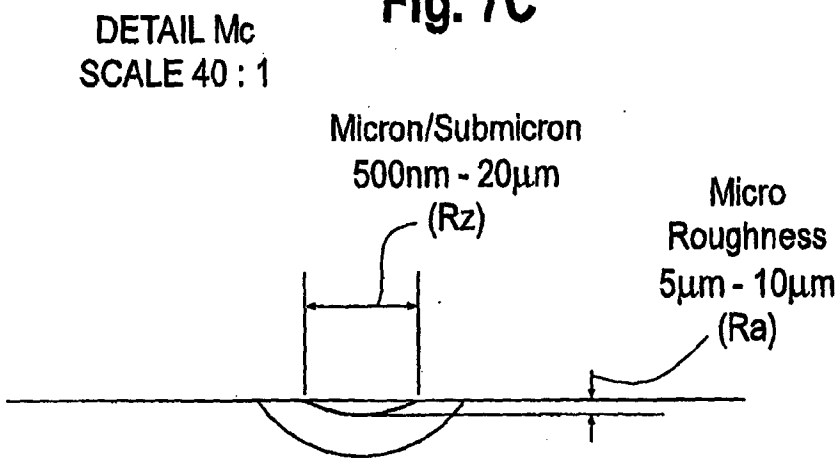

DETAIL Mc
SCALE 40 : 1
Micron/Submicron
500nm - 20µm
(Rz)
Micro
Roughness
5µm - 10µm
(Ra)

Fig. 7D

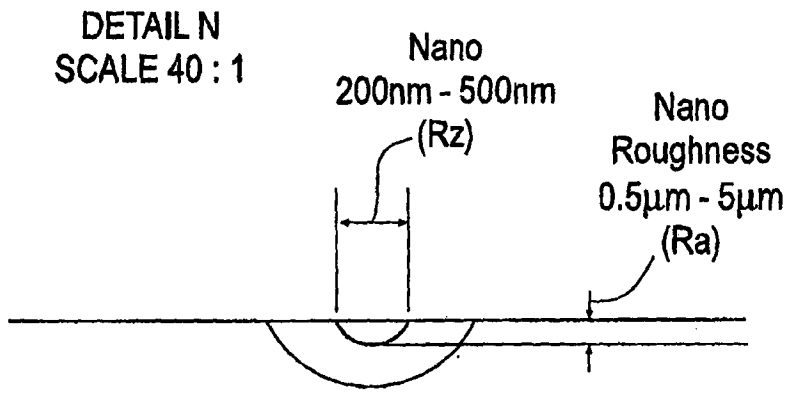

DETAIL N
SCALE 40 : 1
Nano
200nm - 500nm
(Rz)
Nano
Roughness
0.5µm - 5µm
(Ra)

Fig. 8

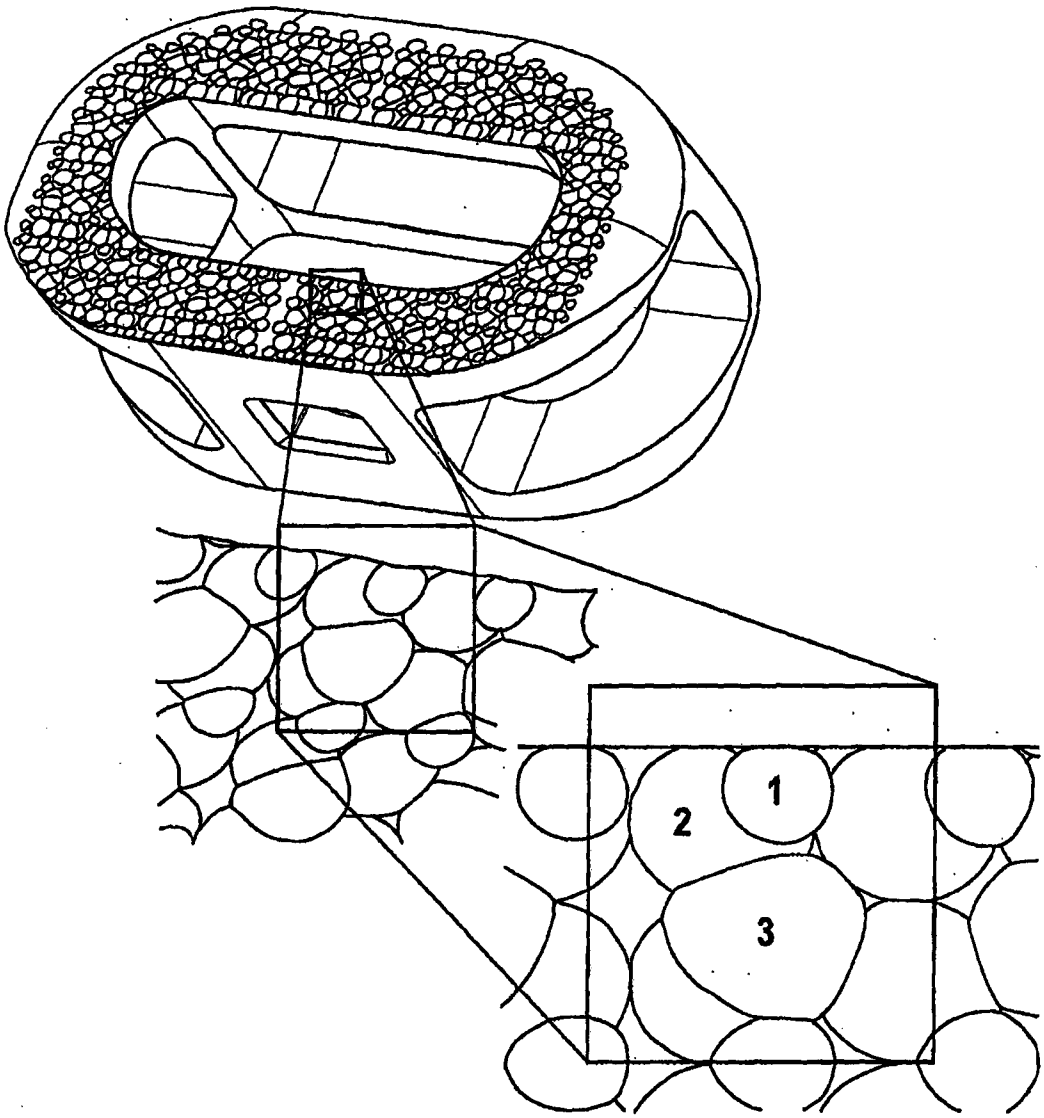
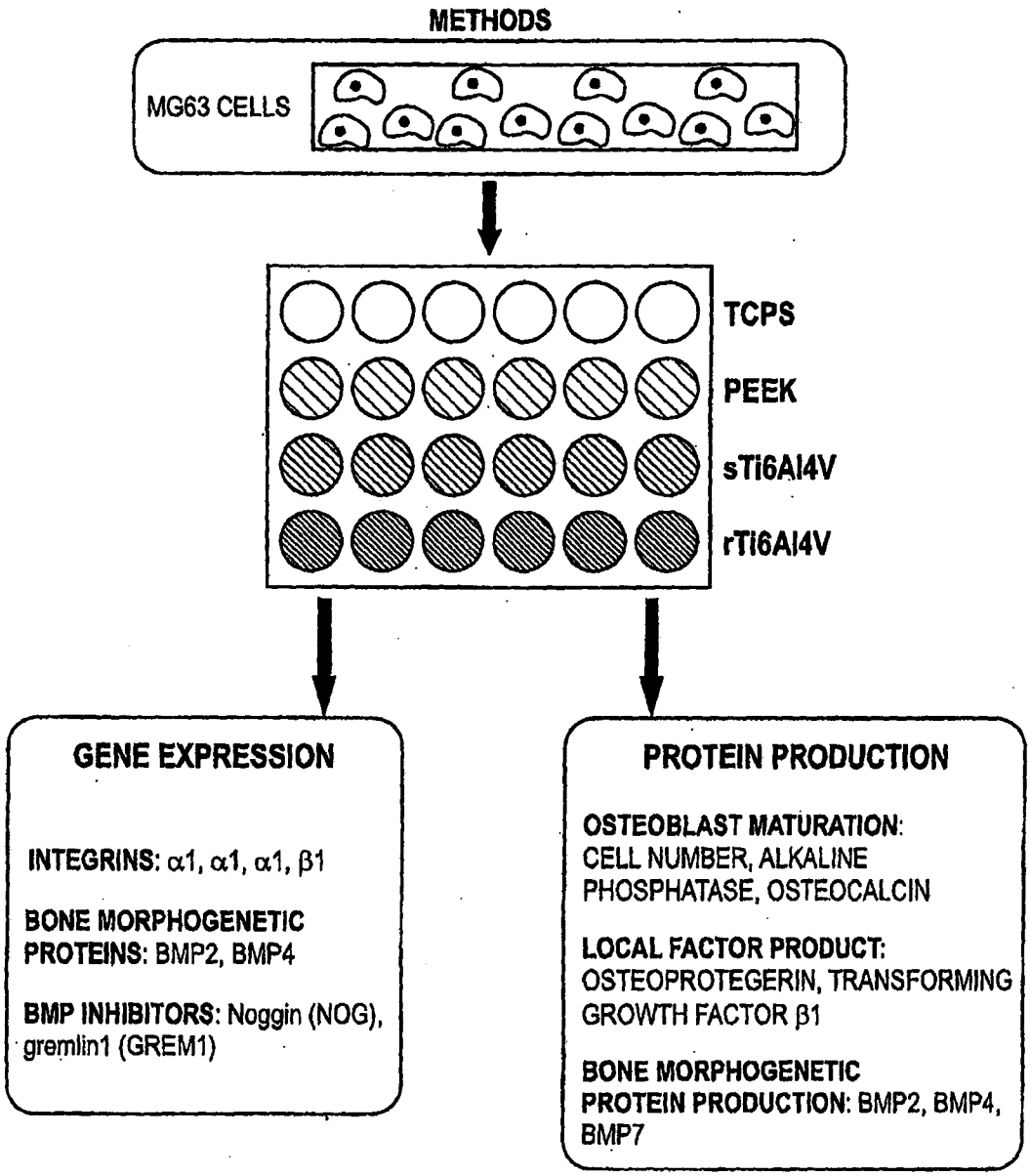


Fig. 9


METHODS
MG63 CELLS
TCPS
PEEK
sTi6Al4V
rTi6Al4V
GENE EXPRESSION
INTEGRINS: α1, α1, α1, β1
BONE MORPHOGENETIC PROTEINS: BMP2, BMP4
BMP INHIBITORS: Noggin (NOG), gremlin1 (GREM1)
PROTEIN PRODUCTION
OSTEOBLAST MATURATION: CELL NUMBER, ALKALINE PHOSPHATASE, OSTEOCALCIN
LOCAL FACTOR PRODUCT: OSTEOPROTEGERIN, TRANSFORMING GROWTH FACTOR β1
BONE MORPHOGENETIC PROTEIN PRODUCTION: BMP2, BMP4, BMP7

Results of Osteogenic Markers

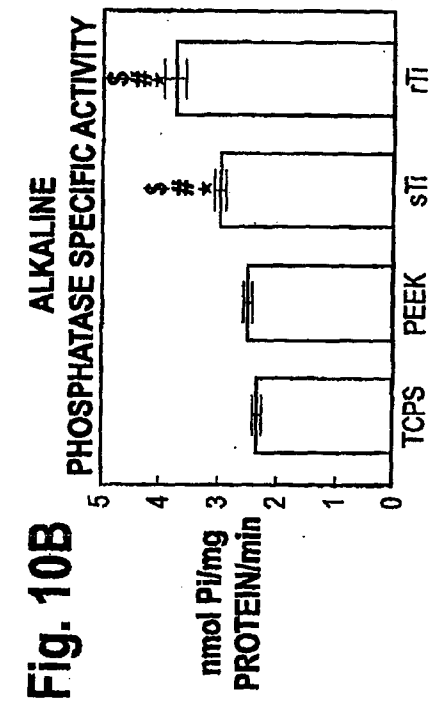


Fig. 10B

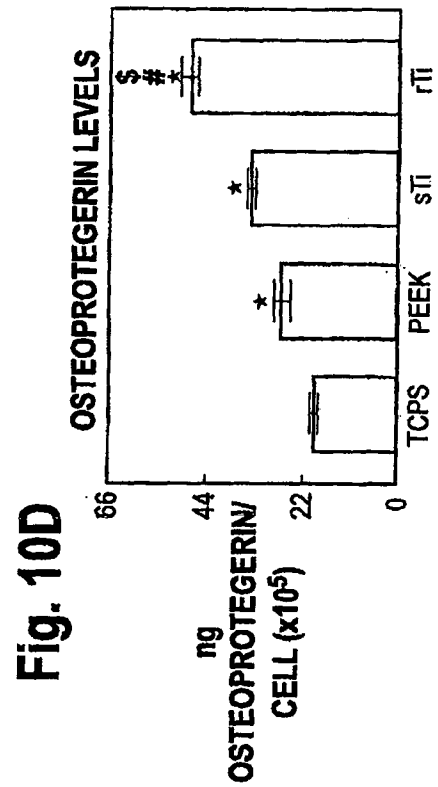


Fig. 10D

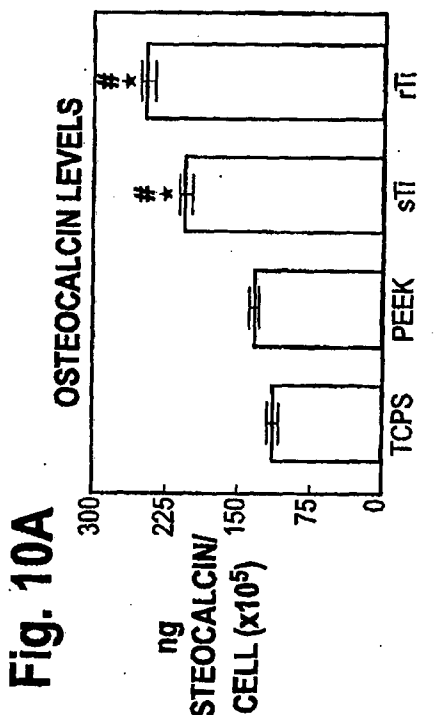


Fig. 10A

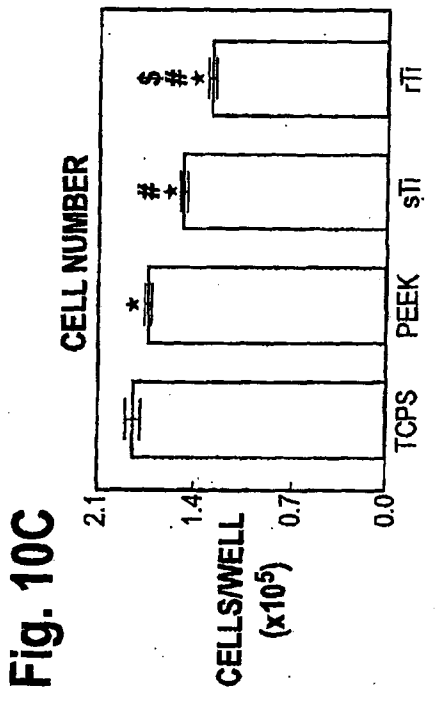


Fig. 10C

Cytokine Analysis - BMP and TGFβ

Fig. 11A

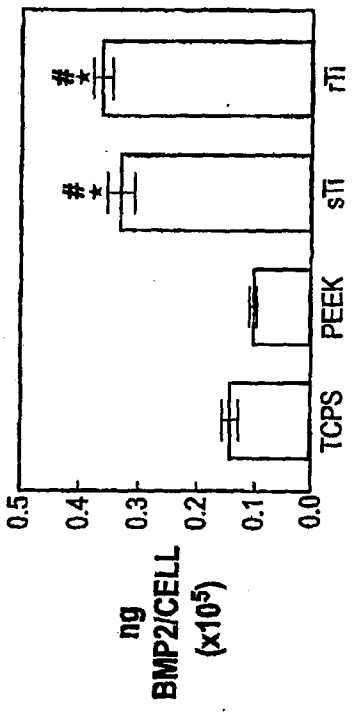


Fig. 11B

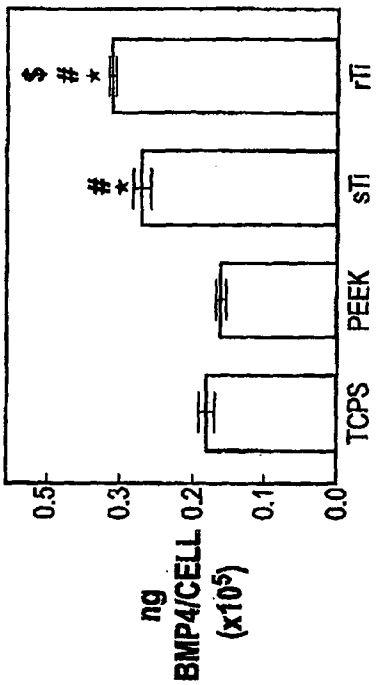


Fig. 11C

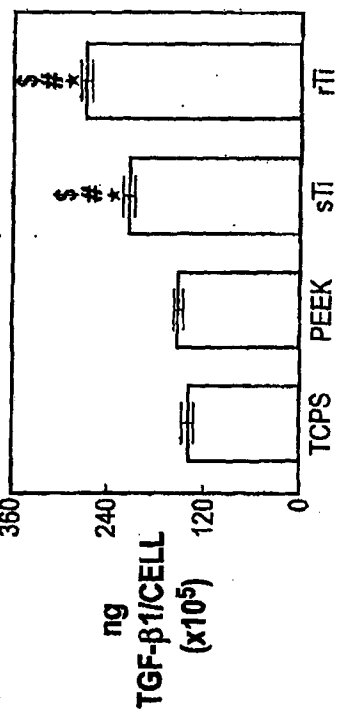
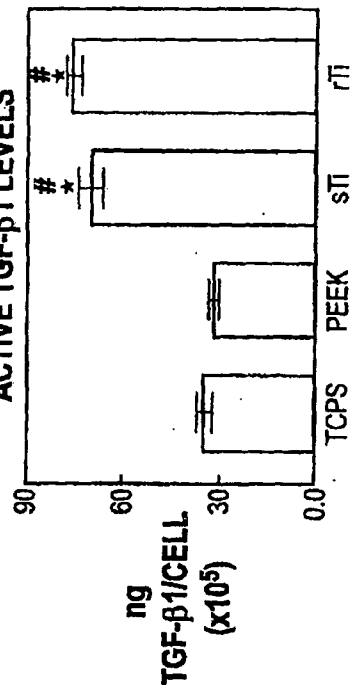


Fig. 11D



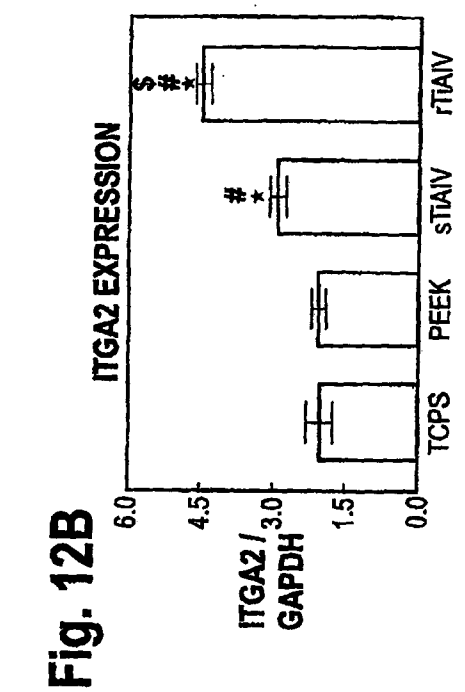


Fig. 12B

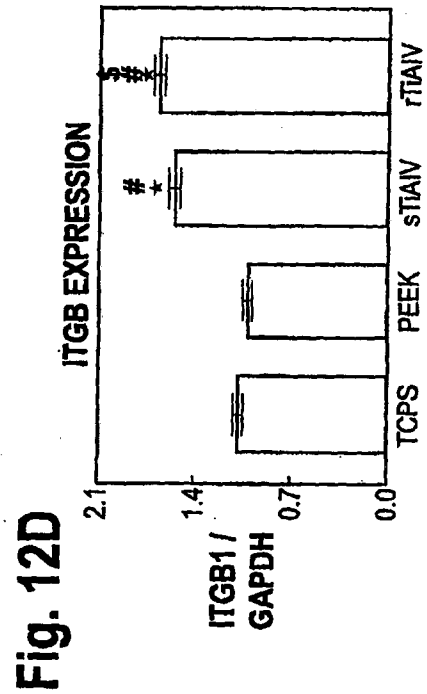


Fig. 12D

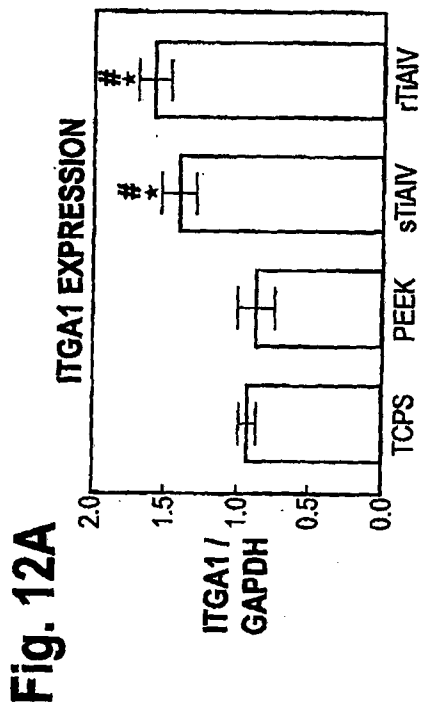


Fig. 12A

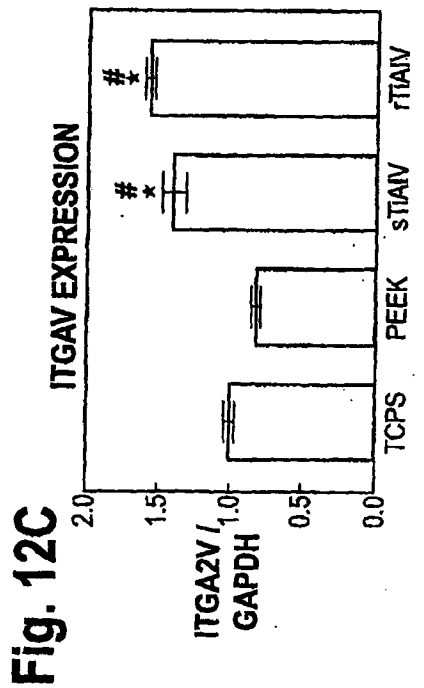


Fig. 12C

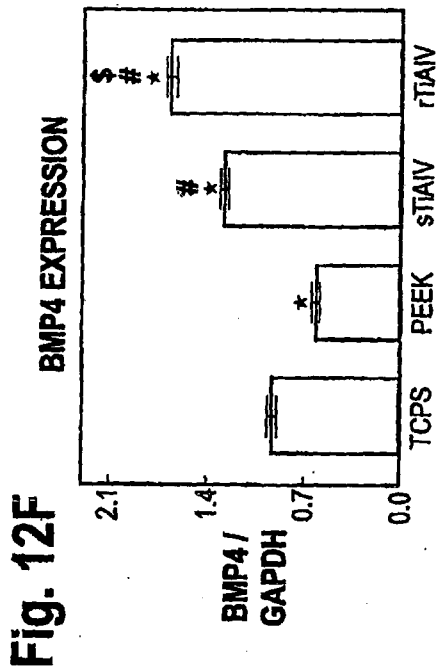


Fig. 12F

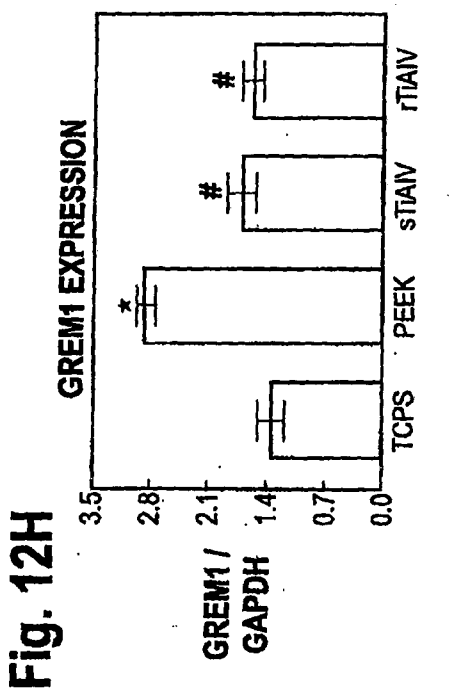


Fig. 12H

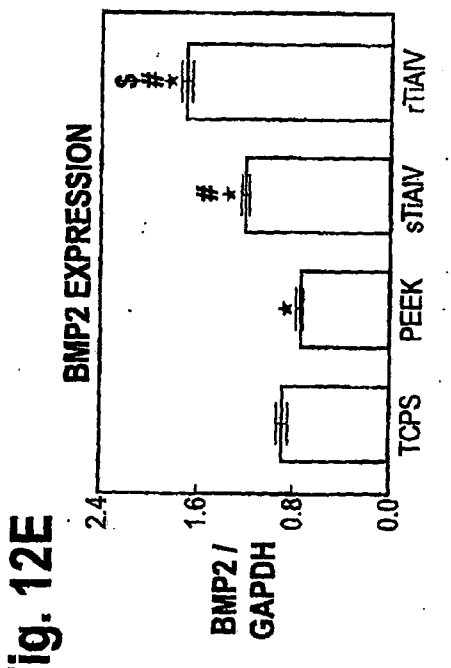


Fig. 12E

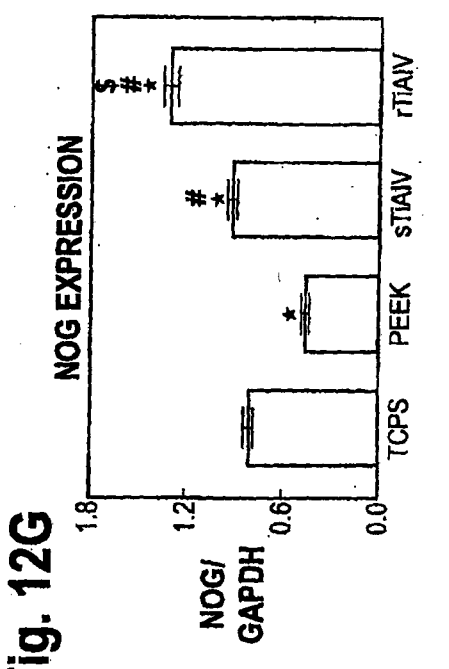


Fig. 12G

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/022192

A. CLASSIFICATION OF SUBJECT MATTER

A61F 2/44(2006.01)i, A61B 17/70(2006.01)i, A61F 2/30(2006.01)i

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)

A61F 2/44; A61F 2/28; A61F 2/02; A61C 008/00; A61B 17/88

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

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

eKOMPASS(KIPO internal) & Keywords: vertebral, disc space, repeating, three-dimensional, pattern, depth, in-growth, biocompatible, surface, implant

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007-0282441 A1 (STREAM, K. et al.) 06 December 2007 See abstract; figures 44,45,51; claims 1-6.	1-10
A	US 2007-0270956 A1 (HEINZ, E. S.) 22 November 2007 See abstract; figures 1-22; claims 1-17.	1-10
A	US 2001-0039454 A1 (RICCI, J. et al.) 08 November 2001 See abstract; figures 1-28.	1-10
A	US 2006-0093646 A1 (CIMA, M. J. et al.) 04 May 2006 See abstract; figure 2C.	1-10
A	US 2005-0147942 A1 (HALL, J.) 07 July 2005 See abstract; figures 9,10.	1-10
A	US 7018418 B2 (AMRICH, M. et al.) 28 March 2006 See abstract; figure 13.	1-10

☐ Further documents are listed in the continuation of Box C.

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