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(54) **Title:** A SCALABLE MATRIX FOR THE *IN VIVO* CULTIVATION OF BONE AND CARTILAGE

(57) **Abstract:** The present invention provides implantable receptacle devices (and methods) for use in bone and tissue regeneration which provide immediate structural stability and strength to a zone where tissue regeneration is required. By virtue of their size, shape and construction, the devices are scalable, modular, structurally stable, self-stacking in three dimensions, can be aggregated to an anatomically accurate shape, and hold various materials delivered into the implant area so as to create a highly regenerative micro-environment. They can be implanted via less invasive surgical procedures, and because they act as external scaffolding as well as being imbedded as an integral part of a matrix for the effective and rapid regeneration of bone and cartilage *in vivo*, they may provide significant advantages to patients or subjects in terms of reduced pain, faster healing and fewer complications.

A SCALABLE MATRIX FOR THE *IN VIVO* CULTIVATION OF BONE AND CARTILAGE

FIELD OF INVENTION

The present invention relates to an implant system for the *in vivo* regeneration of stable bone and cartilage, and in particular to devices specifically shaped as receptacles for scaffold constructs which together form a stable matrix for the regeneration of bone and cartilage *in vivo*.

BACKGROUND OF THE INVENTION

Bone loss is a major problem in trauma and orthopaedic surgery. Everyday, surgeons have to deal with the challenge of patients with major bone loss, either due to trauma, cancer, congenital defects, previous surgery or failed joint replacements.

Bone tissue is composed of a matrix that primarily consists of collagen protein, but is strengthened by deposits of calcium, hydroxyl and phosphate salts, referred to as hydroxyapatite. Inside and surrounding this matrix lie the cells of bone tissue, which include osteoblasts, osteocytes, osteoclasts and bone-lining cells. All four of these cell types are required for building and maintaining a healthy bone matrix, as well as remodelling of the bone under certain conditions.

Most importantly, bone is an extremely dynamic and well organised tissue, from the modulation of the hydroxyapatite crystal arrangement at the molecular level to the strain pattern of the trabecular network at the organ level. The synergy of the molecular, cellular and tissue arrangement provides a tensile strength comparable to that of cast iron, with such an efficient use of material that the skeleton is of surprisingly low weight for such a strong supporting structure

At the microscopic level bone consists of 2 forms: woven and lamellar. Woven bone is considered immature bone and is usually found in the new-born or in fracture callus (healing bone). Lamellar bone is more organised and begins to form 1 month after birth. Thus, lamellar bone is a more mature type of bone that results from the remodelling of immature woven bone. The highly organised, stress oriented collagen fibres of lamellar bone give it anisotropic properties – that is, the mechanical

behaviour of lamellar bone differs depending on the orientation of the applied force, with its greatest strength parallel to the longitudinal axis of the collagen fibres.

Injury, disease and developmental defects can all result in bone defects that require bone grafting procedures, where new bone or a replacement material is placed in apertures around a fractured bone, or in bone defects. Bone grafting allows bone healing by filling the gap, or merely provides mechanical structure to the defective bone, through the provision of artificial material that is not incorporated into a patient's own bone.

Autograft may be used where it is appropriate to take the patient's own bone tissue from another site in the body, usually the iliac crest, although bone from the distal femur, proximal tibia or fibula may also be used. Autograft has advantages: it provides osteoconductivity (i.e., the graft supports the attachment of new osteoblasts and osteoprogenitor cells). Furthermore, it provides osteoinductivity, or the ability to induce non-differentiated cells into osteoblasts.

In the context of autograft for injuries such as bone fractures, the grafting procedure can be quite complex, and may fail to heal properly. Grafting for bone fractures is generally only considered when a reasonable sized portion of bone has been lost via fracture. In this context, bone grafting may be performed using the patient's own bone, usually taken from the iliac crest, or using bone from a donor (allograft). The replacement bone is usually held in place by physical means (e.g., screws and pins), while the healing process occurs.

The drawbacks for autograft procedures include surgical complications (e.g., acute and chronic pain, inflammation, infection), and limitations in relation to the amount of bone that can be harvested for grafting. Furthermore, complications occurring after bone grafting include fracture at the donor site after cortical graft removal, intra-operative bleeding and postoperative pain after iliac crest biopsy and stress fractures, hernias through an iliac donor site and gait problems.

The alternative procedure, allograft, where bone graft material is taken from a donor or cadaver, offers some advantages over autograft in terms of the lack of surgical

complications in obtaining the bone graft material. However, there is a risk of disease transmission from the donor to the recipient of the bone graft material, which is not overcome by pre-implantation treatment of the tissue with techniques such as gamma irradiation. Furthermore, the allograft may not knit well with the patient's own bone, leading to weakness at the point of union of the graft. Also, where bone is harvested from a donor, there exist the same risks as harvesting replacement bone from the patient, as discussed above.

A variety of alternative graft materials exist, including ceramic materials, polymeric materials and chemically inert substances. Many of these are commercially available. These bone substitutes are often inoculated with bone marrow and/or growth factors to provide the osteoconductivity and osteoinductivity that is seen when autograft bone is used.

In the case of certain bone substitute materials, there is the disadvantage that they do not become permanently incorporated into a patient's own bone and are thus subject to breakage, loosening and erosion.

While bone grafting using a polymeric matrix or bone graft has been found to have the capacity for bone regeneration (Borden *et al., J Bone Joint Surg Br.* 2004 Nov; 86(8):1200-8; Mankani *et al., Biotechnol Bioeng.* 2001 Jan 5; 72(1):96-107), the site of regeneration will naturally be in a weakened state until full bone mineralisation and osteoblast replacement is attained.

Extracellular matrices for example hydroxyapatite, various metals like magnesium, tantalum or titanium, calcium sulphate, tricalcium phosphate and various polymers have been used for a long time to act as scaffolds, alone or in various combinations and sub-combinations, to facilitate tissue engineering of bone and improve the success of bone grafting procedures. One recent example of prior art in regard to extracellular matrices is US 7,201,917, which also contains numerous references to prior art in the field. The most common disadvantage of these scaffolds, as well as methods of bone grafting, is that the process of healing (repair) or incorporation of the new bone takes weeks or sometimes months; and in that interim period the newly formed bone is subject to breakage, erosion or damage.

As is well known to those experienced and practised in orthopaedic surgery, an additional drawback common to all these grafting procedures is that bone graft or bone graft substitute, when used to fill a defect or gap or space is not as strong as normal bone and therefore needs to be supported by or augmented with an internal or external fixation until healing and remodelling occurs.

Methods for the manipulation of scaffold pore size, porosity, and interconnectivity are considered extremely important to the science and art of bone and tissue regeneration (Ma and Zhang, 2001, J Biomed Mater Res, 56(4):469 477; Ma and Choi, 2001 Tissue Eng, 7(1):23 33). An extensive review of the state of the art in orthopaedic implants and commercially available products reveals that pore size, material, preparation methods and chemical treatment are extensively manipulated in an effort to increase the chances of rapid growth, healing and/ or regeneration. However, whether for bone grafts/ substitutes or for other scaffolding, the possibility of providing "imbedded" structural stability and strength to scaffold materials, or interior reinforcements analogous to reinforced concrete, at an intermediate scale within an implant zone has not been considered adequately.

Numerous other publications and patents have been filed with respect to implants, implant materials and implant design, all addressing the issues within bone and tissue engineering as they are currently understood. In particular, two items of prior art which address unusually shaped "plugs" for orthopaedic use are US Patent 5,861,043 and WO 01/91672 A1. The devices described in these disclosures are principally void-filling plugs which may have different possible shapes. While they provide some structural stability, they are in the main soft and not as hard as cancellous or cortical bone. In fact they should have the same Young's modulus as hyaline cartilage and/ or subchondral bone or they would not work for the purpose they are designed for. In addition, methods of keeping these conjoined or aggregated may be complex or unreliable in surgical practice. Moreover, they are not designed to allow vascularisation or angiogenesis to occur with ease in spaces filled by these plugs. Consequently there still remains a need for improved devices and methods for the genuine regeneration of bone and cartilage, in a manner that is better customised and optimised for the individual patient, and preferably *in vivo*.

In a departure from the above approaches, the devices of our present invention are designed as complex receptacles which self-stack when juxtaposed or pressed together, and reinforce smaller-scale scaffolding in an effective manner while tissue regeneration and healing take place.

Recently there have been reports (Brown RA et al., *Advanced Functional Materials.* 2005;15:1762-1770) of ways in which to speed up controlled engineering of biomimetic scaffolds by rapid removal of fluid from hyperhydrated collagen (or other) gel constructs using plastic compression technology. The huge scale shrinkage in the process allows the introduction of controllable mechanical properties to the construct. Critically, this process takes minutes rather than the conventional days (or weeks) normally necessary to engineer collagen tissue. However, this technology at present can only be used *in vitro* to produce native collagen structures with controllable nano- and micro-scale biomimetic structures. There is a need for creating a reliably osteoinductive and osteoconductive biomimetic construct fabricated by plastic compression which may be implanted. The product of this plastic compression technology still needs to be delivered viably into living systems, and a device or method is required for expanding or scaling it up to dimensions much larger than currently achieved, stabilising it in three dimensions and creating the appropriate biomechanical and cellular environment to enable remodelling and healing. In general, a need also exists for delivering other matrices or scaffolding constructs viably into living systems and expanding or scaling these up to dimensions much larger than currently achieved, stabilising them in three dimensions and creating the appropriate biomechanical and cellular environment to enable remodelling and healing.

OBJECTS OF THE INVENTION

It is an object of the present invention to provide devices (and methods) for use in bone and tissue regeneration which provide immediate structural stability and strength, create a highly osteoinductive and osteoconductive micro-environment, can

be quickly and rapidly scaled up by those practised in the art to a desired shape and dimension, can be implanted via less invasive surgical procedures, and possibly provide significant advantages to patients or subjects in terms of reduced pain, faster healing and fewer complications.

It is another object of the invention to improve postoperative results following reduction and treatment of spinal fractures using minimally invasive techniques.

Further objects hereof are extant although not described.

SUMMARY OF THE INVENTION

The present invention provides a bone and tissue regeneration system, which combines:

A. an implantable device at meso-scale, specifically shaped and designed as a receptacle for
B. biomimetic constructs at nano- and micro-scale, and
C. if necessary an exterior hull or wrapper or mesh at macro-scale that may carry, contain or encapsulate the above mentioned devices and constructs

The basic concept is that there are at least 2 orders of scaffolds:

- (A) a strong, structurally stable, specifically shaped scaffold device to take weight/ load and provide compression resistance, and
- (B) a highly osteoinductive and softer scaffold which makes rapid bone or cartilage ingrowth possible.

The implantable meso-scale devices of (A) provide a *meso-scale scaffold,* and we define "meso-scale" herein as being in the dimension range of one or more micrometres up to tens of millimetres. These implantable devices have been shaped and designed with two purposes:

1. providing the necessary immediate structural strength and stability to the implant zone within the mammalian body where bone or tissue regeneration is required.

2. providing the nano- and micro-scale biomimetic scaffolds or constructs of (B) with a complex interlinked receptacle within which these biomimetic constructs can be juxtaposed or connected together, and grow so that in their final form and position the meso-scale device(s) could be seen as imbedded within, and reinforcing the biomimetic scaffold

Thus the primary but non-limiting purpose of this invention is to form a scalable matrix for the regeneration of bone or cartilage within a mammalian subject. We recognise, however, that the principles described herein may be used for the regeneration of other tissue as well. This meso-scale matrix is intended for intra-osseous space or intra-cartilage space, but may be used elsewhere and in other applications in a mammalian body. The devices providing meso-scale scaffolding possess specific shape(s) and are designed to aggregate or stack into stable interconnected meso-scale receptacles for biomimetic constructs, thus providing scalable osteoconduction within the implant zone.

Further, when a meso-scale scaffold device and biomimetic constructs are combined together and seeded or infused with various cells and growth factors, they form a highly effective, scalable, customised *in vivo regeneration matrix.*

In its most basic embodiment, therefore, the meso-scale scaffold protects the inner softer scaffold until bone or tissue growth is strong enough. The meso-scale scaffold may or may not be removed at a later date. Moreover, inner biomimetic scaffolds may be loaded into meso-scale scaffolds before, during or after surgery.

We also provide here some non-limiting methods for combining and/ or aggregating such scaffolds and constructs as well as an exterior hull at several levels of structure and dimension to create a complete bone or cartilage regeneration matrix which is customised and optimised for the individual patient.

In one aspect, this invention consists of a meso-scale device which when combined with biomimetic constructs by one skilled in the art, is capable of causing clinically significant levels of bone or cartilage regeneration within a patient. In another aspect, this invention comprises the method for combining and deploying the above-

mentioned devices and constructs either in preparation for, and/ or during surgery so as to cause clinically significant levels of bone or cartilage regeneration within a patient.

The implantable receptacle devices, by virtue of their size, shape and construction, have the following properties: they are scalable, modular, structurally stable, self-stacking in three dimensions, can be aggregated prior to or during surgical procedures to an anatomically accurate shape, provide structural integrity to a zone where tissue regeneration is required, are capable of holding and interconnecting various constructs, materials, and biomolecules delivered into the implant area, and act as external scaffolding as well as being imbedded as an integral part of a matrix for the effective and rapid regeneration of bone and cartilage *in vivo*.

It is the shape(s) of the scaffold device/ components which fulfils many of the various functions which are described herein, and makes possible the various properties of the bone and tissue regeneration system. For example, in one non-limiting approach, the biomimetic constructs made by plastic compression may be micro-manipulated into a stable position and conformation/ orientation within the single compartment of the meso-scale scaffold device. When these meso-scale scaffold devices then stack together in 3-dimensional space, their internal compartments are all interconnected in a stable structure which resists deformation, and create a complex interconnected receptacle extending the biomimetic constructs within the intra-osseous or intra-cartilage space, thus allowing cell-mediated remodelling of bone or cartilage tissue to take place throughout the implant area.

DETAILED DESCRIPTION OF THE INVENTION

The present invention arose from the development of devices or a system for treating fractures of the spine or other bone that provides a bone conserving or bone preserving approach and can be done using minimal invasive instruments. It can however be extended as a solution for other tissue as well.

The term "patient" refers to patients of human or other mammal origin and includes any individual it is desired to examine or treat using the device(s) of the present invention. However, it is understood that "patient" does not imply that symptoms are present. Suitable mammals that may benefit from use of the device include but are not restricted to, humans, primates, livestock animals, laboratory test animals, companion animals (eg. cats and dogs) and captive wild animals.

Description of Meso-Scale Scaffolding

The inventors have noted from the literature and personal experience that most bone substitute materials available today, although good at providing osteoconduction (and osteoinduction in some cases), lack the necessary strength to withstand compressive and other forces. Once used, most of these materials do not have the anisotropic properties of bone until healing occurs – a process which takes 6 to 8 weeks.

Certain specific shapes, when applied to bone substitute material, metal or plastic (particularly those made using existing SLM or SLS technology) gain compressive strength through stacking. These shapes may be broadly described as polyhedral. They also self-stack, which we herein define as the tendency to form a stable conjoined structure when aggregated together in close proximity in 3-dimensional space. This property is also present in nature and allows seemingly small discrete structures to build into larger robust structures. However, most polyhedral shapes have been described in Euclidean and other geometry but are seldom found in nature. Moreover, it has hitherto been neither obvious nor simple to fabricate such shapes from available materials. The present invention demonstrates the actual fabrication by SLM of polyhedral shapes that are small, stable, can be easily stacked together and possess several other properties more fully described below.

The primary device, which is a unit of the final meso-scale scaffolding system is a polyhedral receptacle. Those well-versed in this area of mathematics and geometry will know that the term polyhedron may be defined as a three-dimensional object composed of a number of polygonal surfaces, which includes but is not limited to all polyhedra described as Platonic, Archimedean, Kepler-Poinsot, having Tetrahedral/ Octahedral/ Icosahedral symmetry, Non-Convex Snubs, Prisms/ Antiprisms, Johnson

Solids, Near Misses, Stewart Toroids, Pyramids and Cupolae, and Degenerates as well as the compound and/ or stellated versions of all the aforementioned, including also geodesic spheres, geodesic domes or sections of geodesic spheres and domes.

In particular, of all the known polyhedra, some highly preferred shapes are the dodecahedron, the hexagonal prism, the hexagonal antiprism, the pentagonal dipyramid and the tetrahedron (See Figures 1-5).

In a highly preferred embodiment of these and other shapes, the polyhedra are "wireframe"; we define "wireframe" hereafter for the purpose of this invention as follows: an accurate description of a "wireframe" meso-scale polyhedral scaffolding device is that the substance/material of construction of the polyhedron resides only along the edges encompassing each polygonal face of the polyhedral shape; the rest of the polyhedral shape is empty or hollow and can be filled with other substances. In other words, they are polyhedral receptacles. Expressed another way, the ratio of space to substance in these "wireframe" polyhedra is in excess of 80:20 (Figures 1-6). However, as described below, other embodiments may not have the same space: substance ratio.

In another preferred embodiment, the polyhedron may be partially "filled" in any manner by its material of construction, rather than be completely "wireframe"; for example, a dodecahedral shape may appear to be part "filled" with its own material of construction in any manner desired; or it may have some of its faces removed to create a "basket" (see Figure 7). In an obvious variation of these embodiments, the polyhedron may be completely "filled" by its material of construction but be porous in nature, and/ or adsorptive or absorbent in function.

In another highly preferred embodiment, by virtue of their material of construction, the polyhedra may be either "wireframe" or full-face, and may be first unfolded to a flattened, planar, polygonal shape; and/ or they may be folded from this flattened planar polygonal shape to any other complex topology or shape by several random or directed folds, all with the purpose of minimally invasive surgical implantation. In one non-limiting example of this embodiment, the polyhedra are constructed from nitinol, which confers many of the above properties on the device. Thereafter, the

polyhedra thus treated may be left in any shape or topology, or re-folded to their original shape, and this process may be carried out before, during or after the surgical implantation, so that the meso-scale scaffold(s) perform their required function in the regeneration matrix (as described in the section, "Construction of a Scalable Tissue Regeneration Matrix", below). One non-limiting version of the step-wise unfolding and refolding is depicted in Figure 9.

In a variation of the preceding embodiment, by virtue of their material of construction, the polyhedra may be significantly and reversibly compressed to a much smaller volume with the purpose of minimally invasive surgical implantation, and thereafter may be caused to regain their original dimensions and shape during or after the implantation to perform their required function in the regeneration matrix (as described in the section, "Construction of a Scalable Tissue Regeneration Matrix", below).

In one non-limiting example of a typical method of use of all the above embodiments, a composite or aggregate formed of a multitude of discrete polyhedra, which can each be any size upwards of 1 micrometre in any one dimension, and stacked together in 3-dimensional space, forms the required interior scaffolding or reinforcement within a given bone or cartilage undergoing repair or regeneration; in other words, this composite of discrete stacked polyhedra fills out the intra-osseous or intra-cartilage space where repair or regeneration is needed (See Figure 6).

Obviously, any assortment of polyhedra in a single or multiple shapes, whether solid, partially filled or hollow, using any appropriate metal, plastic, polymer, or other material capable of retaining 3-dimensional shape, and in any assortment of sizes ranging upwards from 1mm in any one dimension, may be packaged together into a kit which allows a surgeon skilled in the art to select the exact size, dimensions, shape and scale of meso-scale scaffolding required by a patient for surgical implantation.

In the most preferred process, the polyhedra of the aforementioned embodiments are fabricated by selective laser melting (SLM). See Figures 8a-8d, which show photographs of an SLM plate prior to excision of very small polyhedra (1.5mm –

2.1mm). However, the polyhedra may also be formed by other methods and processes of solid fabrication, rapid prototyping (particularly selective laser sintering or SLS), or extrusion, or nano-assembly, or nano-construction, or gel formation and hardening etc.

Construction of a Scalable Tissue Regeneration Matrix

In a preferred embodiment and related method of constructing such an embodiment, the (single) compartment(s) found within each of the "wireframe" polyhedra or partially "filled" polyhedra are loaded with collagen sheets assembled into spirals, formed by the process of *plastic compression.* These collagen spirals themselves are known to contain biomimetic structures at nanometric and micrometric scale (Brown RA et al., *Advanced Functional Materials.* 2005;15:1762-1770).

In a preferred variation of the above embodiment, the collagen sheets or micro-spirals manufactured by plastic compression are first seeded with any combination of biologically functional cells, such as but not limited to stem cells, fibroblasts, osteoblasts, osteocytes, chondrocytes etc., and/ or other materials such as fibronectin or hydroxyapatite or other polymers; and then in one preferred process, this composite collagen construct is loaded within the polyhedral compartments and then cell-cultured *in vitro* ; and in another preferred process, this composite collagen construct is loaded within the polyhedral compartments and implanted surgically to allow remodelling and healing entirely *in vivo.*

In yet another preferred process, any of the above embodiments or constructs may be perfused, injected, seeded, or washed or filled with biologically functional cells such as but not limited to fibroblasts, osteoblasts, osteocytes, chondrocytes, soft tissue cells, endothelial cells, blood cells, immune cells or stem cells, (whether autologous or exogenous), and/ or preparations of biomolecules such as growth factors (e.g., TGF-β superfamily, BMP-1, etc.).

In one preferred variation, any of the above embodiments of the tissue regeneration matrix may be coated with antimicrobial peptides or other drugs and medications. In another preferred variation, any of the above embodiments of the tissue regeneration

matrix may be used as a delivery system or vehicle for the emplacement of slow-release drugs or other bioactive molecules.

In another preferred embodiment, any aggregation of polyhedra at any level and in any shape, and in any of the embodiments described above, may be wrapped in a polymer, preferably biodegradable, so as to enable the entire construct to be delivered into an intra-osseous, subperiosteal or bone surface zone or cartilaginous zone to promote bone or cartilage regeneration.

In all these embodiments, their variations and through the accompanying methods and processes, the polyhedra provide structure and stability at meso-scale, from ten(s) of micrometres to several tens of millimetres. Thus the collagen-loaded polyhedra become a significant enabler of tissue regeneration at multiple scales: nano-, micro- and milli-. Since the polyhedra can themselves be manufactured in various sizes, and also stacked, the entire tissue regeneration system of the present invention is highly and precisely scalable in the hands of a surgeon skilled in the art.

The inventors view this special combination of scalable and stackable polyhedral receptacle devices, biomimetic collagen constructs and cells/ growth factors as a true tissue regeneration "matrix", as distinct from an inert or biologically inactive scaffold. Since the nano- and micro-scale structures of the plastic-compressed collagen spirals are held in extensively interconnected compartments in 3-dimensional space by wireframe polyhedra, they can be scaled outwards or expanded in three dimensions and stacked stably within the intra-osseous or intra-cartilage space in a manner which allows perfusion with fluids, media, gels, blood and filling with any other materials of choice. Thus this invention is designed to maximise osteoinduction, osteoconduction, osteogenesis and the chances of angiogenesis/ vascularisation, extensive cellular remodelling and the ultimate healing of the bone or cartilage *in vivo*.

Materials and Nature of Construction of the Scalable Tissue Regeneration Matrix

This scalable matrix, particularly the exterior hull and meso-scale scaffold devices, may be fabricated from a wide range of clinically approved or accepted biocompatible

materials, such as metals and their alloys (titanium, cobalt chrome, stainless steel, nitinol, etc.), ceramics (hydroxyapatite or tricalcium phosphate) or polymers (polylactide, polyglycolide, polyetheretherketone, etc.), or bioactive glasses (Bioglass, Biogran etc.), or any combination of these or other materials which may be approved for such uses. The materials may be combined so as to allow the polyhedral receptacles to either remain implanted and inert, or degraded by natural processes, or allow them to be completely or partially resorbed into the mammalian body.

In one preferred embodiment, the meso-scale receptacle devices may be aggregated into a kit comprising an assortment of polyhedra fabricated from a single material. In another embodiment, the meso-scale devices may be aggregated into a kit comprising an assortment of polyhedra fabricated from different materials. In yet another embodiment, the polyhedra may be fabricated from one material but loaded, embedded, packed, coated, lined or infused with one or more other materials to confer upon the stacking structure a plurality of osteoinductive and osteoconductive properties. All these embodiments may be presented variously alone or in combination in a multitude of commercially available kits.

In yet another preferred form, some components of the matrix may be inserted into the polyhedra in gel or semi-fluid form, which can then harden when they are activated by a UV light or other similar light source.

In yet another preferred form, any or all of the above embodiments of the scalable tissue regeneration matrix may be constructed of or include porous materials, or deliver such materials into the zone where bone and cartilage regeneration is required.

In still another preferred form, any or all of the above embodiments of the scalable tissue regeneration matrix may be nano-assembled, or nano-textured or nano-surfaced by methods known to those skilled in the art so as to further enhance the osteoinductive and osteoconductive properties of the scalable tissue regeneration matrix.

Properties, Features and Benefits of the Scalable Tissue Regeneration Matrix

Preliminary and simple studies and fabrications by the inventors have shown that the polyhedral shape of the meso-scale scaffold, particularly when made at millimetric scales by SLM, has several properties and features:

1. The polyhedra 'flow' as a series of discrete particles when pushed through MIS channels into a surgical (fracture or bone defect) site, or through any of the mammalian body's own channels, spaces or vessels.
2. They self-stack in three dimensional space to fill out or form any shape which is robust, i.e., resists deformation, provides immediate structural integrity and helps load-bearing
3. By aggregating/ stacking within larger polyhedra, they can be scaled upwards either continuously or step-wise into dimensions of a few cubic centimetres. In one non-limiting example, there can thus be multiple sizes, and multiple types of polyhedrons within the same construct. In one non-limiting example, a large icosahedron at 8mm could contain or be packed with several dodecahedrons at 2mm.
4. They can be stacked easily during surgery within any existing or created void, aperture or gap in bone or tissue structure by the surgeon using visualisation aids (for example image intensifiers, endoscopy and fluoroscopy)
5. They can also be aggregated and stacked prior to insertion or implantation into a fracture or defect site

The meso-scale scaffolds have several benefits:

- they decrease or eliminate the need for artificial void creation within a fracture zone, as the scaffolds act as an imbedded, internal sub-structure stacking around and holding the bone fragments together, and/ or translating and elevating compression fracture zones and encourage bone healing
- they increase the stability and structural integrity within fracture zones as well bone graft sites due to their ability to interlock at various levels.
- enable high, precise control of fracture reduction particularly in small bones and intra-osseous damage zones
- no increase in internal tissue pressure or aggravation of the molecular/ immunological stress which accompanies cell damage.
- low chance of diffusion, migration, dislodgement or deformation after surgery

- increased chances of angiogenesis due to the higher proportion of available or "empty" space in the construct
- increased chances of cell-mediated remodelling

Description of Exterior Hull

The exterior hull may be either a mesh-like or lattice-like reticulated single construction, made by any method of fabricating solids, and may encapsulate, surround, circumscribe, be adjacent to, or contiguous with the fracture zone, bone defect or bone loss area where structural integrity is needed and bone repair or regeneration are to be carried out.

In a most preferred embodiment, the exterior hull is built to the anatomically accurate shape of the bone or cartilage which is to be repaired or regenerated, in the precise dimensions and orientation required by the patient requiring such repair or regeneration. In a preferred method for making the above embodiment, the exact shape and dimensions of the required bone or cartilage are obtained from X-rays or 3D CT scans of the patient, or other similar imaging technology such as MRI or PET scans etc., which may be readily available, and the exterior hull is customised to the exact shape required using computer design or CAD software.

One major design variation of the above embodiment is that on its inner surfaces, the exterior hull may be inlaid with polyhedral recesses or "niches" capable of receiving and holding aggregations or stacks of meso-scale scaffolding devices in a stable position.

The exterior hull is made as a single free-form entity without the need for joining or articulating separate pieces. In a particularly preferred process, the external scaffolding is made by selective laser melting (SLM). It may also be formed by other methods and processes of solid fabrication, rapid prototyping, or extrusion, or gel formation and hardening etc.

In another preferred embodiment the exterior hull may be soft and pliable and be made of a sheet of polyglycolic acid or polycaprolactone or collagen or any combination or sub-combination of these and other biomimetic substances.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1a: Schematic drawing of a dodecahedron as wireframe
Figure 1b: Unfolded net of dodecahedron
Figure 2a: Schematic drawing of a hexagonal prism as wireframe
Figure 2b: Unfolded net of hexagonal prism
Figure 3a: Schematic drawing of a hexagonal antiprism
Figure 3b: Unfolded net of hexagonal antiprism
Figure 4a: Schematic drawing of a pentagonal dipyramid
Figure 4b: Unfolded net of hexagonal antiprism
Figure 5a: Schematic drawing of a tetrahedron
Figure 5b: Unfolded net of hexagonal antiprism
Figure 6a: Several "filled" dodecahedra stacked together in 3 dimensions
Figure 6b: Wireframe view of stacked dodecahedra
Figure 7: A partially "filled" dodecahedron with interior compartment
Figure 8a – 8d: Photographs of an SLM plate showing rows of built polyhedra prior to excision or harvest
Figure 9: Unfolding of a dodecahedron into a flat polygonal planar shape and step-wise re-folding into a dodecahedron
Figure 10: View of the Ilium and its structure
Figure 11a and 11b: Bone harvest zone on the ilium, and area to avoid

METHODS AND EXAMPLES OF USE

The use, application and methods pertaining to the scalable matrix will be further understood by reference to the following non-limiting examples:

Example 1: Treating Lumbar Compression or Burst Fractures.

The traditional way of treating these fractures is to perform a Vertebroplasty or Kyphoplasty in the case of compression fractures and in the case of burst fractures of the spine requiring surgical intervention to achieve biomechanical stability, to perform a combined anterior instrumentation and short segment posterior instrumentation (SSPI). In low grade burst fractures, Vertebroplasty plus SSPI may provide a less invasive method of stabilising the burst fracture but there have been no conclusive tests or patient trials showing that this method is stable. Moreover there is a risk of cement or existing bone substitute materials leaking out and injuring the spinal cord, nerves or blood vessels.

It is important to note that vertebral burst fractures are typically associated with high impact axial loading resulting from trauma.

Surgical Instructions

Step One

Place the suitably consented and anaesthetised patient prone on a montreal mattress.

Step Two

Reduce the fracture and stabilise using Short Segment Posterior Instrumentation of your choice. The rods will bridge the fractured vertebra.

Step Three

Make sure the spinal canal is adequately decompressed and remove any loose bone fragments.

Step Four

Option1

Stack or pack spaces in the fractured vertebra with the scalable matrix, inserted through the pedicle allowing the matrix to do its job and create a stable interlock. This is done under fluoroscopic control.

Option 2

Stack or pack spaces in the fractured vertebra with the scalable matrix, inserted through the extra-pedicular approach allowing the matrix to do its job and create a stable interlock. This is done under fluoroscopic control.

Step Five

Once a stable construct is obtained, wash, obtain haemostasis and close in layers. Use a redivac drain for 24 hours.

Example 2: Correction of Various Structural Defects

a. Fill the defects in the talar dome of the ankle following post traumatic osteochondral fractures where there is a large hole. Scalable matrix is filled into the curetted holes.

b. Fill the defects in surface of the knee where there are defects/holes following osteochondritis dissecans. Place the matrix into the curetted holes.

c. Fill the defects in the mid portion of the scaphoid bone where there is an established non-union with a large defect which needs filling before a screw is placed.

d. Following avascular necrosis of the femoral head there is a large cavity which could be filled with the matrix prior to placing a re-surfacing metallic femoral head.

Example 3: Maxillofacial Surgery

In maxillofacial surgery augmentation procedures, the scalable matrix could be used. One particular example is sinus floor augmentation; however all bone cavities such as those from tooth extractions, cysts, fractures or defects after tumour removal can be filled using the scalable matrix.

Example 4: Bone graft harvesting

The traditional way of harvesting bone graft from the pelvis is associated with a high complication rate. The reason is that the graft is taken by an incision over the iliac crest with a vertical segment of iliac bone removed. But apart from the region of the

ASIS and PSIS the ilium is tissue-thin here (Figure 10), and post-harvest, it bleeds and collapses. The bulk of iliac bone is found just below (2cm) and parallel to the iliac crest; by the ASIS and the PSIS. This is where the bone graft should be harvested; the hatched area should be avoided (Figures 11a and 11b).

Surgical Instructions

Step One

Place the patient prone/ supine (face down or face up) or lateral (on their side) - surgeon's preference. Place a 1cm incision below the outer prominence of the PSIS or ASIS. Place the guide though small bony entrance, parallel to crest and radiate downwards from ASIS or PSIS.

Step Two

Pass bone harvester subperiosteally over guide a distance of **up to 5cm.**
Remove the cuttings. (OR pass the dowel cutter over the guide wire.
Cut dowels in multiple directions.
Remove the dowels).

Step Three

Place a suction catheter down the channel/dowel the holes and suck out the bone marrow including stem cells.
Fill gap with bioabsorbable space material

Step Four

Option1

Pass a bougie down the dowel holes and expand the periosteal sleeve
(there is the option to pre-contour the matrix). Then pack the dowel holes with Scalable Matrix

Option 2

Pass the bougie shaped as tibial shaft bone, femoral head, lower femur, upper tibia, proximal humerus, then expand, then pack with Scalable Matrix.
Harvest when mature bone formed (assess either by X-ray, bone scan or biopsy).

While all the disclosures herein are susceptible to various modifications and alternative forms, specific exemplary embodiments of the invention have been shown by way of example in the drawings and have herein been described in detail. It should be understood, however, that there is no intent to limit the disclosure to the particular forms disclosed, but on the contrary, the intention is to cover all modifications, equivalents, and alternatives falling within the spirit and scope of the disclosures. Various combinations and subcombinations and features may be practiced with or without reference to other combinations, subcombinations and/or features, alone or in combination, in the practice of the invention, and, moreover, numerous further adaptations and modifications can be effected within its spirit, the literal claim scope of which is particularly pointed out as follows.

There are a plurality of advantages of the present disclosure arising from the various features of the devices, kits and methods described herein. It will be noted that alternative embodiments of the devices, kits and methods of the present disclosure may not include all of the features described yet still benefit from at least some of the advantages of such features. Those of ordinary skill in the art may readily devise their own implementations of an apparatus and method that incorporate one or more of the features of the present disclosure and fall within the spirit and scope of the present disclosure.

CLAIMS

We claim:

1. A receptacle built or formed in the shape of any known polyhedron, with a size upwards of 1 micrometre along any of its dimensions, formed precisely by any method of rapid prototyping (particularly selective laser melting and/ or selective laser sintering), or any other fabrication, assembly, extrusion or casting method capable of creating precise three-dimensional shapes using metals, alloys, polymers, ceramic, plastic, gel, or other solid or viscous fluid material, and any combination thereof, for the purpose of implantation directly or indirectly into a cavity, gap, surface or other independent space or zone within the bone or cartilage or other tissue of a mammalian subject where regeneration of bone or cartilage or other tissue is required.

2. The device of Claim 1, which is further characterised in that:
   a. The term "polyhedron" includes but is not limited to those described as Platonic, Archimedean, Kepler-Poinsot, having Tetrahedral/ Octahedral/ Icosahedral symmetry, Non-Convex Snubs, Prisms/ Antiprisms, Johnson Solids, Near Misses, Stewart Toroids, Pyramids and Cupolae, and Degenerates as well as the compound and/ or stellated versions of all the aforementioned, including also geodesic spheres, geodesic domes or sections of geodesic spheres and domes,
   b. it is capable of being placed, projected, pushed, driven or embedded directly into an intra-osseous or intra-cartilage or other tissue void individually, in a group or in a discrete particulate flow through a catheter, channel or other similar device; or it may be introduced through other parts of the mammalian subject's body such as but not limited to airways, bowel (upper or lower), ureter, urethra, vagina; or may be placed subcutaneously; or introduced/ lodged into its desired location through the bloodstream and
   c. by virtue of its shape, it occupies a stable 3-dimensional volume which is load-bearing and not easily deformed when biomechanical pressure

within ranges normal in a mammalian body is applied along multiple planes or axes

3. The device of Claims 1 and 2, wherein the polyhedron thus formed is a solid shape filled out with the substance(s) or material(s) of its manufacture.

4. The device of Claims 1 and 2, wherein the polyhedron thus formed is partially "filled" with the substances or materials of manufacture, leaving some facets and any partial volume of its interior void and empty as a receptacle for other substances.

5. The device of Claims 1 and 2, wherein the polyhedron thus formed has one or more of its facets consisting of its substances or materials of manufacture but is hollow within, as a receptacle for other substances.

6. The device of Claims 1 and 2, wherein the polyhedron thus formed has only its edges consisting of its substances or materials of manufacture, leaving its facets and interior void and empty so that a finite compartment or receptacle for other substances is delimited by, or contained within a "wireframe" which frames or defines the polyhedron.

7. The devices of Claims 5 and 6, wherein the interior of the polyhedral receptacle may comprise multiple finite compartments and/ or other constructs such as a small rod or plate internally, and tenon protruding externally or mortise recessed into the confines of the polyhedral shape.

8. The devices of Claims 1-7, wherein the polyhedral receptacle devices are nano-constructed, nano-assembled and/ or be self-assembling and/or self-replicating.

9. The devices of Claims 5-8, wherein the polyhedron is capable of being reversibly unfolded into either a flat polygonal net or plate, or any other intermediate shape formed by partial or compound folding or unfolding of such a net or plate; or the polyhedron may be reversibly compressed; and thereafter

may be folded back into its original shape, or decompressed to its original shape or dimensions, all by virtue of being made from shape-memory alloys or polymers.

10. The method of Claim 9, wherein any and all such steps of unfolding or re-folding and compression or decompression, or any combination thereof, may take place in any sequence of steps either *ex vivo* or *in vivo*, and either before, during or after a surgical procedure for the implantation of the devices of Claims 5-7, and wherein such folding, unfolding, compression or decompression may be caused by a series of mechanical manipulations and/ or alterations in physical/ chemical environment of the polyhedron.

11. The devices of Claims 1-9, wherein the material of the polyhedra is sintered and porous in nature.

12. The devices of Claims 1-9, wherein the material of the polyhedra is coated or adsorbed with antimicrobial peptides, antibiotics, other peptides, or nano-structures, or other biologics or biomolecules.

13. The devices of Claims 1-9, aggregated as a plurality of polyhedra, which are able to naturally and randomly interlock or stack when placed together in proximity, or can be stacked deliberately together, in a 3-dimensional conformation where each polyhedron has each or most of its facets contiguous with or aligned with at least one facet belonging to another polyhedron, and where the "fit" may be tight, leaving no interstitial spaces, or "loose" leaving interstitial spaces between the polyhedra, and the final aggregated or stacked composite can have any dimensions or volume or shape required of it.

14. The devices of Claims 4 - 9 in the conformation of Claim 13, wherein the aggregated or stacked polyhedral composite with said interior voids provides a complex interconnected network of compartments in three dimensions which network acts as a meso-scale receptacle of scaffolds or constructs of any description or any material at smaller scales, and the whole of which

composite is characterised by mechanical strength, stability, shape memory and a certain degree of elasticity, or any combination of these characteristics.

15. The devices individually, severally and collectively described in Claim 14, wherein the said internal compartment(s) or interconnected network of compartments in three dimensions forming a receptacle have been filled or loaded with a biomimetic collagen construct fabricated by plastic compression.

16. The methods and steps of Claims 14 and 15 wherein the interconnected network of compartments containing scaffolds or constructs of any description of material, and/ or biomimetic collagen constructs, is imbedded within and enables the said constructs to form a stably supported and immobilised matrix of interconnected scaffolds or constructs in 3-dimensional space in a mammalian subject within any zone of the subject's body requiring bone or cartilage or other tissue regeneration.

17. The devices of Claim 15, wherein the matrix of collagen constructs and stacked polyhedra contains soft tissue cells and/or endothelial cells and/or blood cells and/or immune cells, and/or stem cells, and/or other biologically functional cells as may be necessary.

18. The method of Claim 17, whereby the biologically functional cells may be seeded into the devices of Claim 15 either prior to fabrication, aggregation/ stacking, folding/ unfolding (hereafter, "formation") of said devices, or after formation of said devices, or by injection/ insertion after formation but prior to implantation in a mammalian subject, or by injection/ insertion after formation and implantation in a mammalian subject.

19. The devices of Claims 15 and 17 wherein the matrix of collagen constructs and polyhedral receptacles is infused with any of the TGF-β superfamily of ligands, or with the BMP-1 family of proteases by injection/ insertion after formation but prior to implantation in a mammalian subject, or by injection/ insertion after formation and implantation in a mammalian subject.

20. The methods of Claim 17, wherein the seeded cells are cultured in the collagen construct loaded into the polyhedron and/ or stacked polyhedra *in vitro* and prior to implantation.

21. The methods of Claim 17, wherein the seeded cells are grown/ differentiated within the collagen construct loaded into the polyhedron and/or stacked polyhedra *in vivo* after implantation.

22. The devices of Claims 4 - 9, wherein the polyhedral receptacles may be loaded or filled with carriers or delivery systems for slow-release drugs, medicaments, or other biologically active molecules, as well as various polymers, glues or other inorganic molecules.

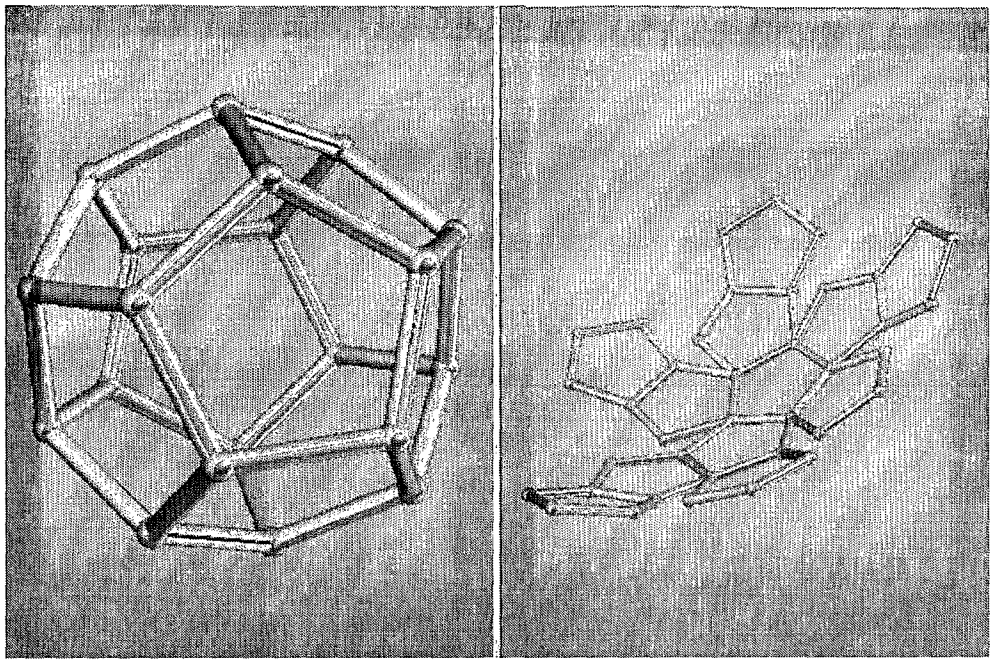
23. A composite device comprising a resorbable polymer wrap placed around any of the devices in Claims 3-9, 11-15, 17, 19 and 22 for the purpose of implantation into a zone requiring bone or cartilage or other tissue regeneration.

24. A composite device formed by embedding/ packing/ stacking any of the devices in Claims 3-9, 11-15, 17, 19 and 22-23 within niches or recesses cut into the interior surfaces of an exterior casing device or hull, which is a mesh-like or lattice-like reticulated single construction, made by any method of rapid prototyping (particularly selective laser melting or selective laser sintering), and which may itself be implanted so as to encapsulate, surround, circumscribe, be adjacent to, or contiguous with any fracture zone, bone defect or bone loss area or other tissue where structural integrity is needed and bone or cartilage or other tissue repair or regeneration are to be carried out.

25. A kit formed from any combination of the devices of Claims 1- 9, 11-15, 17, 19 and 22-24, wherein the kit contains at least one or more of the devices described therein, but is not limited to containing only these items, and may additionally contain other surgical instruments or devices to enable users to promote bone and cartilage or other tissue regeneration *in vivo*.

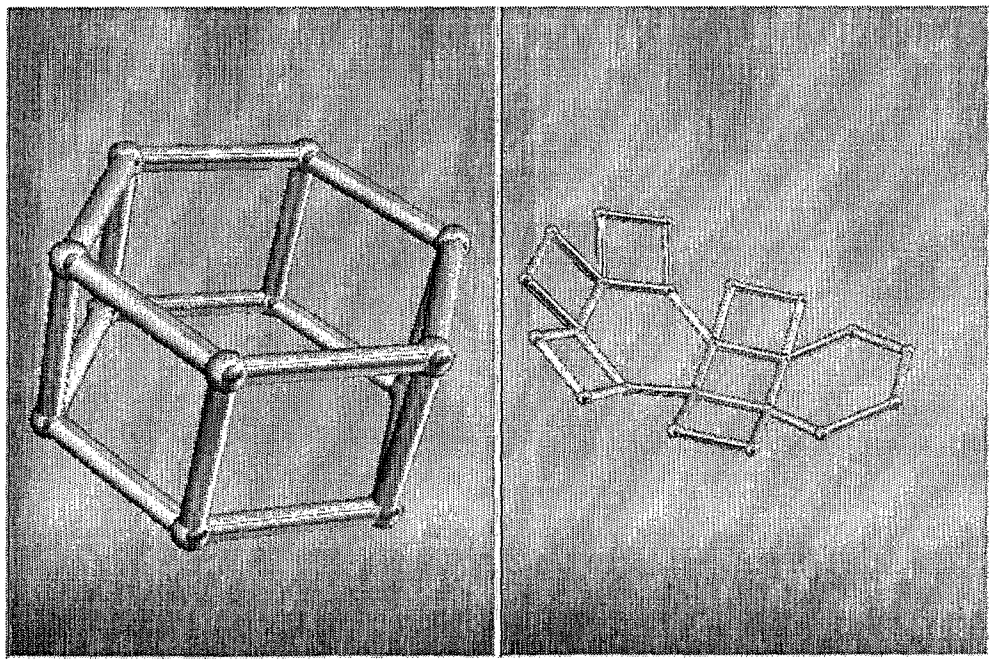
DRAWINGS AND ILLUSTRATIONS

Figure 1



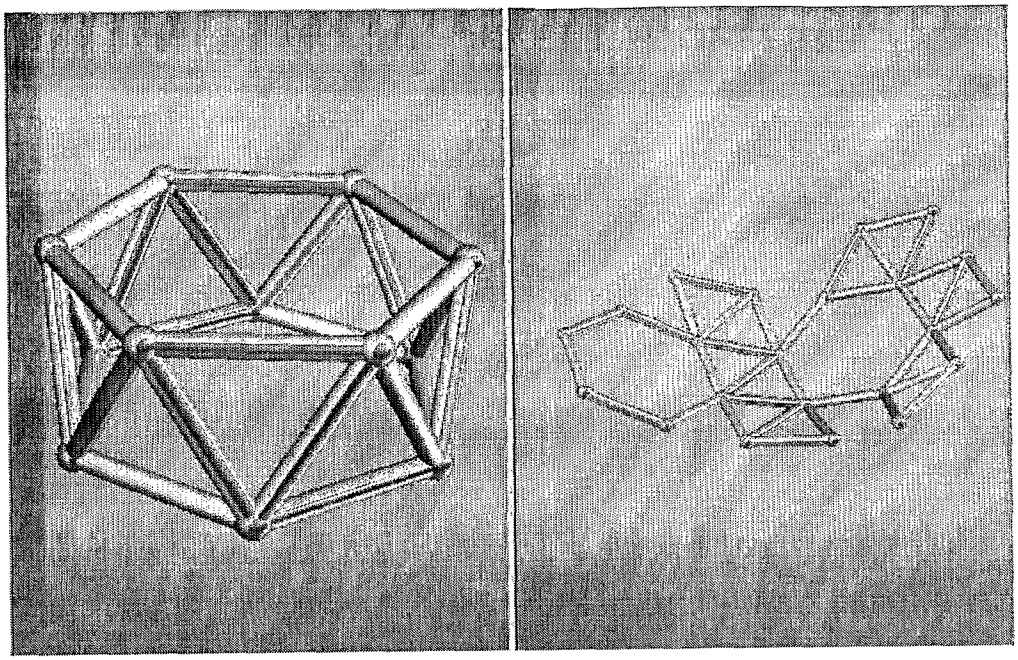
a. Dodecahedron b. Unfolded Dodecahedron

Figure 2



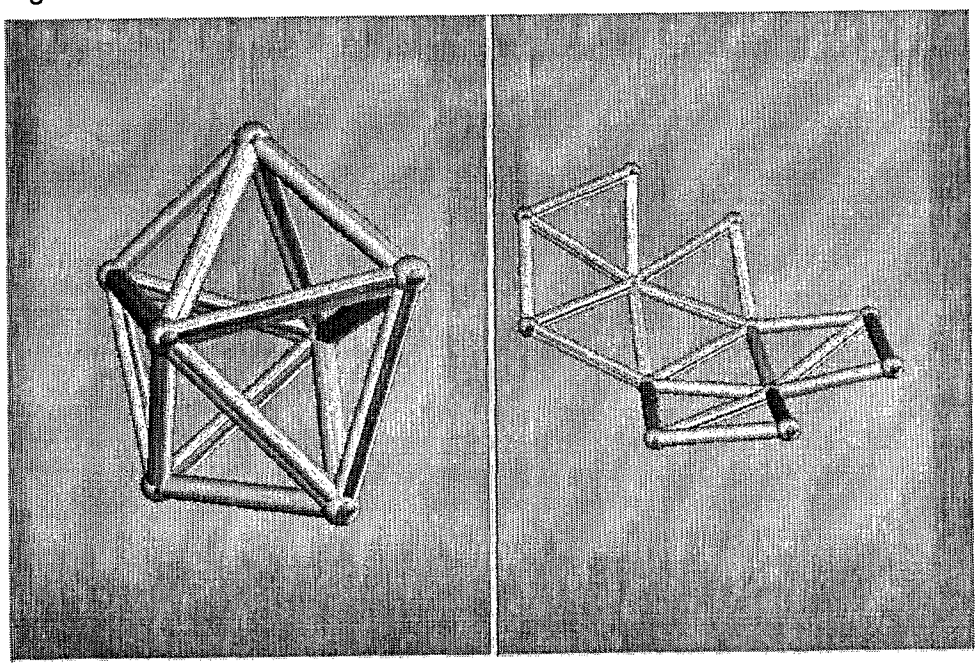
a. Hexagonal Prism b. Unfolded Hexagonal Prism

Figure 3



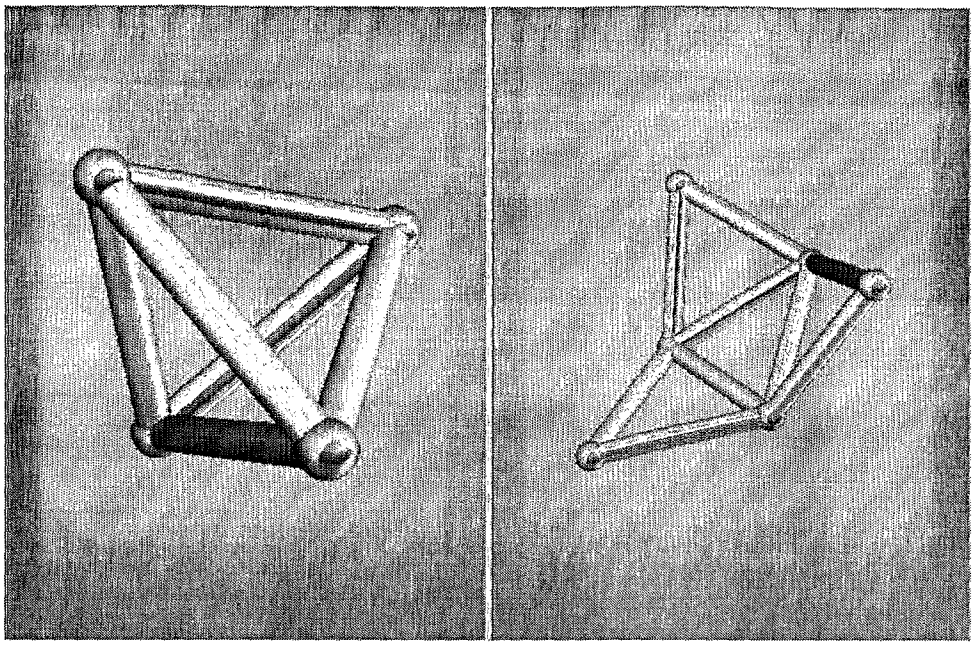
a. Hexagonal Antiprism b. Unfolded Hexagonal Antiprism

Figure 4



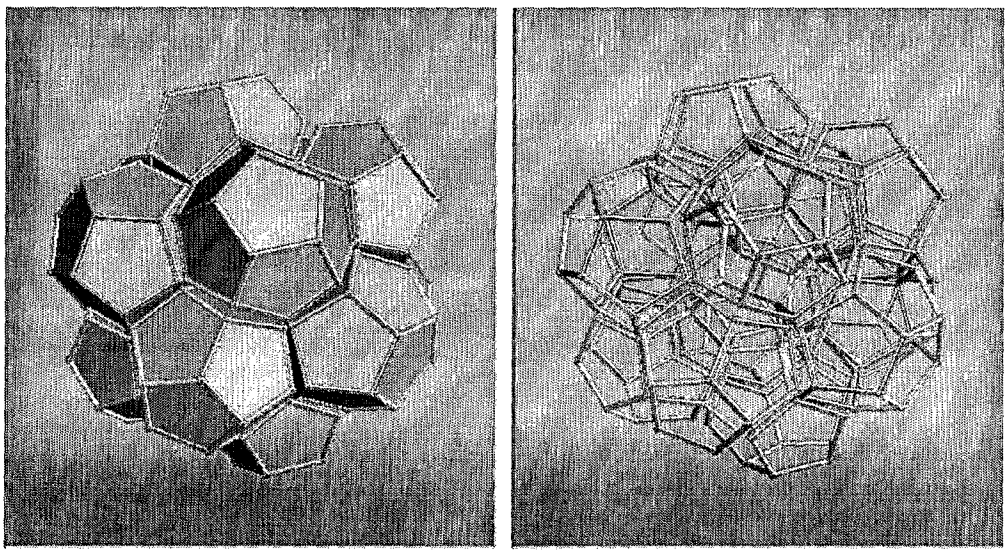
a. Pentagonal Dipyramid b. Unfolded Pentagonal Dipyramid

Figure 5



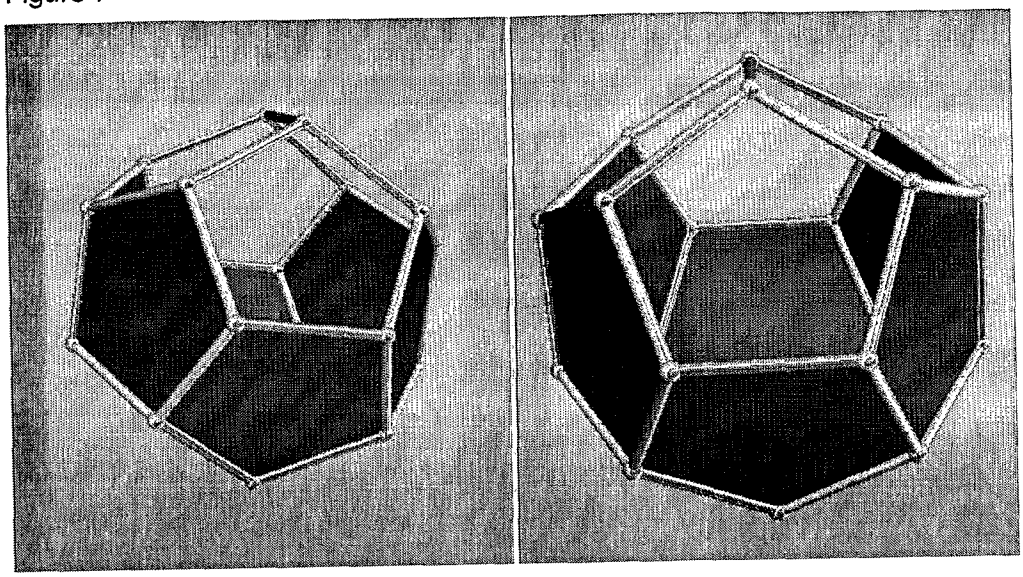
a. Tetrahedron b. Unfolded Tetrahedron

Figure 6



a. A stack of dodecahedra b. A "wireframe" view of stack

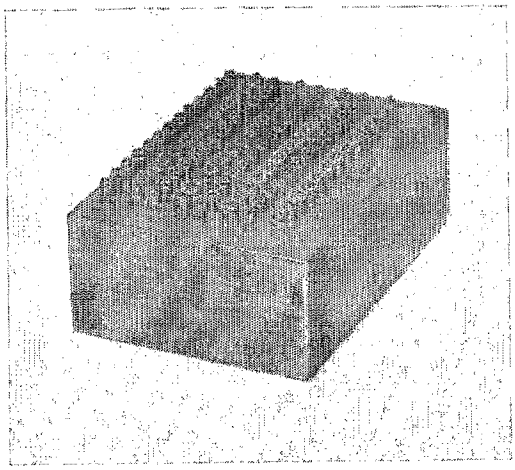
Figure 7



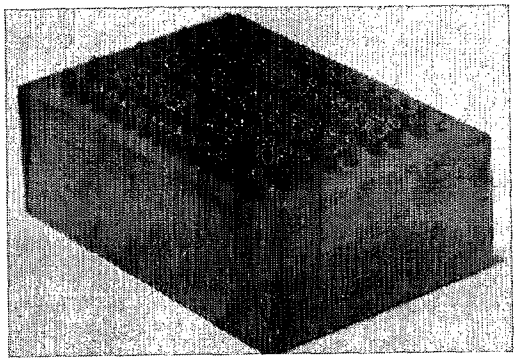
Two views of a "basket" formed when a dodecahedron has some faces removed. The interior of this basket may be filled or empty.

Figure 8

Two rows of built polyhedra on a single SLM plate:
Shown are dodecahedra and hexagonal prisms built from stainless steel

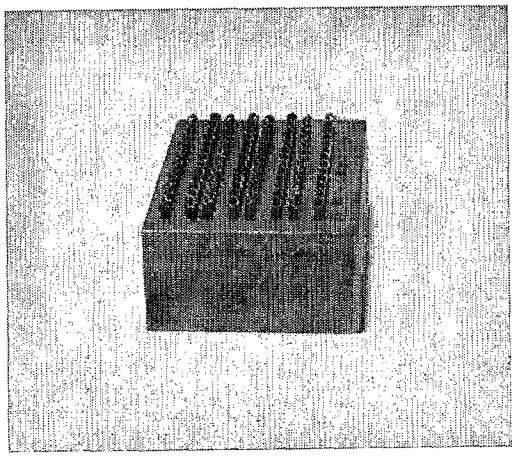


a.

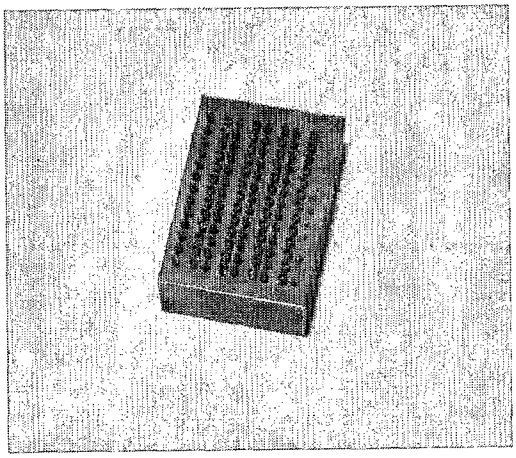


b.

Figure 8 cont'd: End and top views of the SLM Plate. The polyhedra are next "harvested" or excised from the plate and sorted



c.



d.

Figure 9: A simple version of folding/ unfolding

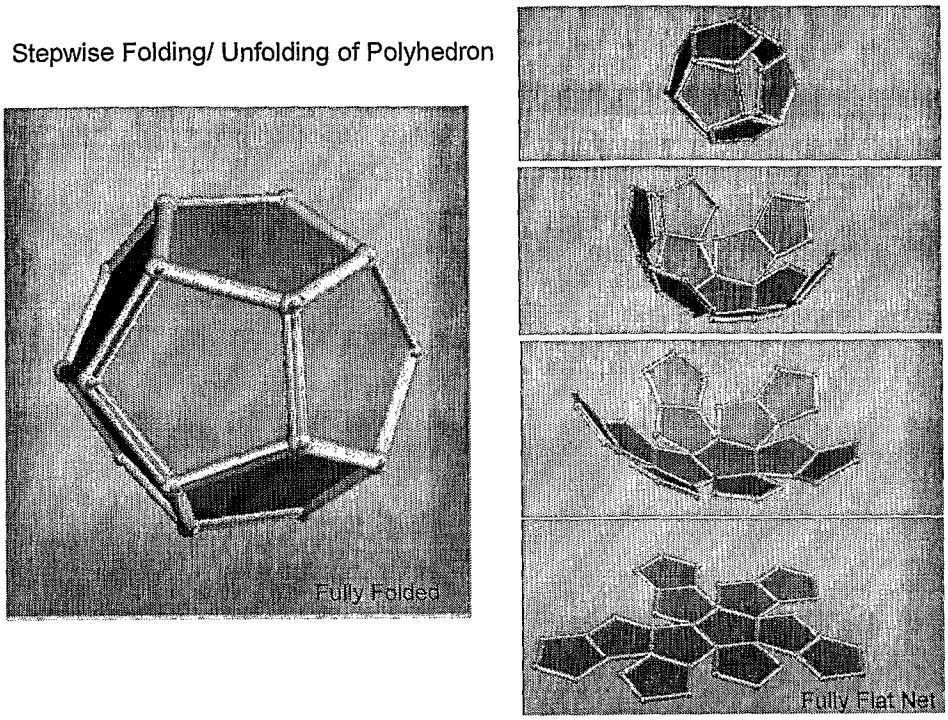
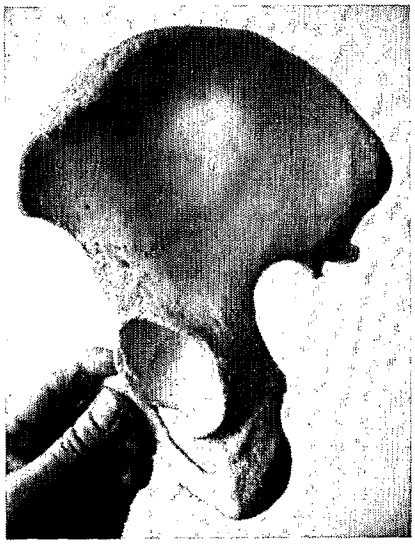
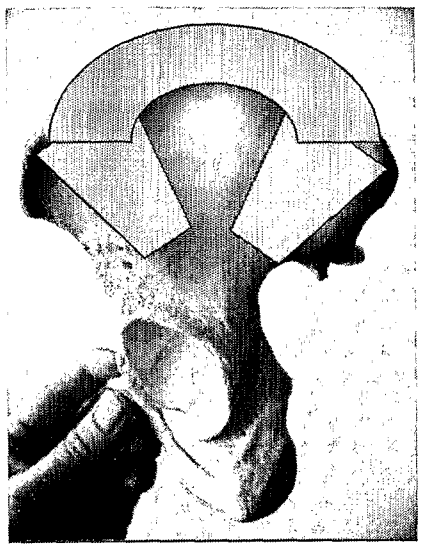


Figure 10

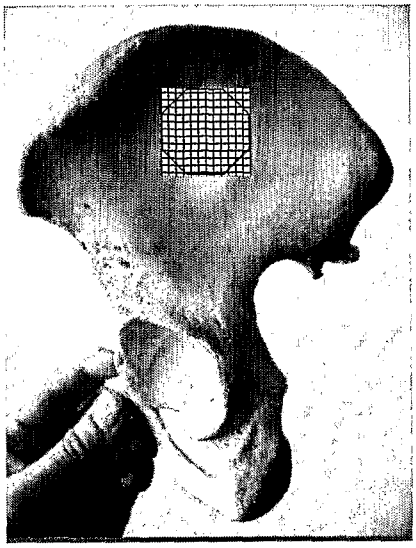


A view of the Ilium

Figure 11



a. Harvest Area



b. Area to avoid

INTERNATIONAL SEARCH REPORT

International application No.
PCT/MY2007/000066

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

A61K 9/00 (2006.01) ***A61K 31/00*** (2006.01) ***A61L 31/00*** (2006.01)
A61B 17/00 (2006.01) ***A61K 38/00*** (2006.01) ***A61L 33/00*** (2006.01)
A61F 2/00 (2006.01) ***A61L 27/00*** (2006.01)

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)

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)
WPIDS, CAPLUS, JAPIO, MEDLINE; Keywords: bone, cartilage, tissue, osseous, scaffold, repair, rebuild, regrow, regenerat?, receptacle, reservoir, container, matrix, laser?, (solid(w)fabrication), 3-D, (three(w)dimension?), solid, implant, biodegrad?, biocompat?, resorb?; IPC: A61K 9/-, 31/-, 38/-, A61L 27/-, 31/-, 33/-, A1B 17/-, A61F 2/-

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2001/0031254 A1 (BIANCHI J R et al) 18 October 2001 Paragraph 30-32, 37, 49, 51 and 54; Figure 1	1-5, 7, 11-19, 22, 25
X	WO 1999/052356 A1 (CHARLOTTE-MECKLENBERG HOSPITAL AUTHORITY) 21 October 1999 Page 6, line 5-25; page 8, line 16- page 10, line 20; page 12, line 1-9; page 12, line 27- page 14, line 17	1-2, 4-5, 8, 11-20, 22-25

[X] Further documents are listed in the continuation of Box C [X] 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
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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"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
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 December 2007	13 DEC 2007

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/MY2007/000066

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/082524 A2 (WILLIAM MARSH RICE UNIVERSITY) 30 September 2004 Pages 3-9 and Figure 2	1-5, 8, 11-14, 22
X	WO 1996/040002 A1 (MASSACHUSETTS INSTITUTE OF TECHNOLOGY et al, [US]) 19 December 1996 Whole document	1, 3-5, 8, 11-12, 22-23
X	WO 2003/071991 A1 (DEPUY ACROMED INC, [US]) 4 September 2003 Page 3, line 14-26; page 5, line 17-page 7, line 3; page 7, line 19-29	1-5, 9-12, 22
X	Patent abstracts of Japan JP 2004/321065 A (NANO PHOTON KK) 18 November 2004 See abstract. See also machine translation, retrieved 4 December 2007 from JPO website <URL: http://www4.ipdl.inpit.go.jp/Tokujitu/PAJdetail.ipdl?N0000=60&N0120=01&N2001=2&N3001=2004-321065> Paragraph 8-16 and drawing 3	1, 6, 8, 11-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/MY2007/000066

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
US	2001031254	AU	23445/00	AU	27861/01	AU	43150/01
		AU	57495/01	AU	64067/00	AU	64997/00
		AU	92917/01	CA	2350509	CA	2367376
		CA	2379665	CA	2397071	CA	2399762
		CA	2437763	CA	2459050	EP	1128849
		EP	1181060	EP	1202756	EP	1246585
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		EP	1427322	EP	1779868	JP	2006034988
		JP	2007044548	MX	PA01010415	MX	PA02000937
		US	6482584	US	6497726	US	6613278
		US	6652818	US	6690659	US	6765896
		US	6805713	US	6893462	US	6947398
		US	2001018614	US	2002072806	US	2002106393
		US	2002119437	US	2003023304	US	2003027125
		US	2003097179	US	2004115172	US	2004210308
		US	2005096742	US	2005100862	US	2005101957
		US	2005119744	WO	0029037	WO	0054821
		WO	0108715	WO	0150999	WO	0178798
		WO	0182993	WO	0224244	WO	02064180
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Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX