

BIOMIMETIC MATERIALS COMPRISING POLYHEDRAL OLIGOMERIC SILSESQUIOXANES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial No. 60/673,880 filed on April 22, 2005.

BACKGROUND OF THE INVENTION

Biomaterials, as such Polyhedral Oligomeric Silsesquioxanes (POSS) and Polyhedral Oligomeric Silicates (POS), may be fabricated by the incorporation of POSS molecules into material for the purpose of providing a nanoscopic topology which favors cellular modulation, bioavailability, and differentiation.

POSS silanol biomaterials have been seen to initially coordinate to metal and ceramic implant surfaces through hydrogen bonding and further react via the elimination of either hydrogen gas or water to form a thermodynamically favored silicon-oxygen-metal bond. The resulting surface is nanoscopically thin, and may be tailored to produce a uniform mono layer or a porous self assembled network providing a nanoscopic topology essentially free of impurities and controllable through selection of composition, R groups, nanostructure size and topology.

Highly rigid, shape specific, chemically tailorable nanostructures such as POSS molecules are desirable as they coordinate surface characteristics at the nanoscale, and provide a surface that is compatible with all sterilization methods. In vitro immunohistochemistry experiments have shown that certain types of POSS nanostructures cause the proliferation and differentiation of bone stroma cell (BSC) and the deposition of apatite. This proliferation and differentiation of BSC provides an indication that POSS nanostructures of appropriate form are bioactive, and therefore also biocompatible and resorbable. POSS biomaterials may also incorporate amino acid sequences, peptides, phosphates, apatites, carbonates, silicates, and related bioactive elements, chemicals, or reagents in combination with POSS cages functionalized with $R = R^1$ hydrocarbon and $R = R^2$ biologically active groups on the $[(RSiO_{1.5})_7(HOSiO_{1.5})_1]_{\Sigma 8}$, $[(RSiO_{1.5})_6(R(HO)SiO_1)_2]_{\Sigma 8}$, $[(RSiO_{1.5})_2(R(HO)SiO_1)_4]_{\Sigma 6}$, $[(RSiO_{1.5})_4(R(HO)SiO_1)_3]_{\Sigma 7}$ and larger sized cages and cage fragments of formula types such as $[(RSiO_{1.5})_2(R(HO)SiO_1)_4]_{\Sigma 6}$, $(RSi(HO)O)_4$, $(RSi(OH)_2)_2O$.

Field of the Invention

The present invention relates to biomaterials that are enabled by the manipulation and development of POSS, POS, and POMS compounds from readily available and low-cost silicon containing feedstocks. Examples of these low cost feedstocks include but are not limited to: Polysilsesquioxanes $[\text{RSiO}_{1.5}]_{28}$, homoleptic Polyhedral Oligomeric Silsesquioxanes (POSS) $[(\text{RSiO}_{1.5})_n]_{\Sigma\#}$, functionalized homoleptic POSS $[(\text{RSiO}_{1.5})_m(\text{RXSiO}_{1.0})_n]_{\Sigma\#}$, heteroleptic POSS $[(\text{RSiO}_{1.5})_m(\text{R}'\text{SiO}_{1.5})_n]_{\Sigma\#}$, functionalized heteroleptic POSS $[(\text{RSiO}_{1.5})_m(\text{R}'\text{SiO}_{1.5})_n(\text{RXSiO}_{1.0})_p]_{\Sigma\#}$, polyhedral oligomeric silicates $[(\text{XSiO}_{1.5})_n]_{\Sigma\#}$, and POSS fragments $[(\text{RXSiO}_{1.5})_n]$.

As defined by the present invention a "biomaterial" is a material that is intended to interact with biological systems. Biomaterial-tissue interactions are best defined by the following terms: "biocompatible", "bioinert", "bioactive", "biomimetic", "resorbable". Stringently defined, biocompatibility is the ability of a material to extract an appropriate biological response in a particular biological environment. This definition implies that any material placed on or into the body will not be inert and will interact with tissues in a dynamic way, altering both the material and the tissues around it. The biological response to a material is critically dependent on five factors: (i) the composition, (ii) surface structure, (iii) topology, (iv) biology of the host site, and (v) the physicomachanical demands on the material.

Biomaterial-tissue interactions are relevant to a wide variety of applications and treatments. Traditionally, the area of biomaterials has focused on materials which can support or replace lost human tissue, for example in orthopedics (femoral implants), vascular biology (arterial stents), and dentistry (filling materials/implants/material-tooth bonding). Currently biomaterials-tissue interactions have been involved in an area called tissue engineering or bioengineering. Roughly defined, tissue engineering is the manipulation of developmental or wound healing processes to repair or replace lost tissue. In this area, biomaterials have been used as permanent or resorbable scaffolds (for cells or other critical molecules), drug-delivery devices, and barrier materials. For example, cartilage cells may be seeded onto a resorbable scaffold, implanted, and allowed to support cartilage development. In many cases, biocompatibility is critical to the success of these treatment strategies. Recently biomaterials have also been used in more non-traditional applications such as imaging, cosmetics, and nutritional supplements. Esthetic applications include maxillofacial prostheses to restore

1 facial contours after surgical treatment for cancer, or in dentistry to restore tooth esthetics
2 after trauma or dental disease.

3 Nanostructured biomaterials are best exemplified by those based on low-cost
4 Polyhedral Oligomeric Silsesquioxanes (POSS) and Polyhedral Oligomeric Silicates (POS
5 and Polyhedral Oligomeric Metallasesquioxanes). POSS, POS, and POMS systems contain
6 hybrid (i.e., organic-inorganic) compositions in which the hollow internal cage like
7 framework is primarily comprised of inorganic silicon-oxygen bonds. The exterior of the
8 nanostructure is covered by both reactive and nonreactive organic functionalities (R), which
9 ensure compatibility and tailorability of the nanostructure with man-made and biological
10 tissues. These and other properties and features of nanostructured chemicals are discussed in
11 detail in U.S. Pat. Nos. 5,412,053 and U.S. Pat. No. 5,484,867 to Lichtenhan et al., both are
12 expressly incorporated herein by reference in their entirety.

13 Significant opportunity exists for technology that can form compatible interfaces
14 between man-made and biological systems. The need is especially acute for prosthetic
15 implants. The U.S. market for total and partial joint replacement is an ever-growing market
16 with over 500,000 procedures being preformed each year in a \$2 billion industry. An
17 important and growing component of this market is the use of bioactive compounds, and
18 surface treatments. Materials such as metals, ceramics, and polymers have been used for
19 decades in an effort to reduce foreign body reaction and increase integration with limited
20 success.

21 Of key importance is the fundamental fact that the interaction between solid surfaces
22 and biological systems are critically important to this field. In general, only the surface of an
23 implanted material is in direct contact with the host tissue, and thus this portion of the
24 material plays a critical role in long term fixation and biocompatibility.

25 Many prior efforts have been made to compatibilize the surface of implants with
26 biological systems. These efforts have included numerous compounding, grafting, and
27 coating methods employing polymeric, single - multiple layer and ceramic coatings (see U.S.
28 Patent Nos. 6,444,318 and 6,069,295). The promise of polyhedral oligomeric silsesquioxane
29 for biocompatible materials lies in their rigid shape, tailorable R group, highly dispersive
30 nature, and hybrid inorganic-organic three-dimensional structure which provides a specific
31 surface area and topology. The also havethe ability to provide stereospecific delivery of
32 reactive groups such as silanol (Si-OH) groups to promote attachment. The ability of

1 polyhedral oligomeric silsesquioxanes to provide specific surface coverage (metals, glass,
2 etc.) to substrates to nonbiological substates has been shown in U.S. Patent No. 5,858,544.

3 Moreover, the most promising property of nanostructured chemicals (POSS, POS,
4 POMS) lies in their ability to rationally control surface area, volume, and roughness. This
5 control in turn affords the ability to stimulate biological response at nanoscopic dimensions,
6 such as the initiation and formation of cellular bonding and response such as apatite, the
7 major inorganic component of bone. It has been seen that the inability of current implant
8 formulations and coatings (such as titanium, titanium-based alloys, and inorganic bio-
9 ceramics) to mimic the physicochemical, mechanical interface, and nanometer geometry
10 found in bone results in inefficient and incomplete bonding, and crack propagation to
11 juxtaposed bone (*i.e.* insufficient osseointegration and substrate failure). By controlling
12 implant surface area and roughness with the present invention, osseointegration is promoted
13 and provides mechanical stability to the implant *in situ*, minimizes motion-induced damage to
14 surrounding tissues, and is imperative for the clinical success of bone implants.

15 Bonding of an orthopaedic implant to juxtaposed bone (*i.e.* osseointegration) is a
16 critical characteristic that determines implant efficacy. Osseointegration is necessary to
17 stabilize the prostheses *in situ* so that physiological loading conditions can be supported and,
18 consequently, the patient can lead a normal, active life. Incomplete osseointegration of
19 prostheses can be caused by surface properties that (i) do not promote cellular adhesion, (ii)
20 do not support new bone growth, or (iii) have mechanical properties that do not match those
21 of surrounding bone tissue. Mismatch of mechanical properties between an implant and
22 surrounding bone can lead to stress and strain imbalances that cause implant loosening,
23 failure, and eventual surgical removal.

24 Unfortunately, current material formulations utilized as bone prostheses (*e.g.*
25 commercially pure titanium, Ti-6Al-4V, and Co-Cr-Mo alloys) do not simultaneously satisfy
26 the surface and mechanical requirements necessary for increased implant efficacy. This is not
27 surprising since, historically, these materials were developed for applications other than to
28 serve as implants (such as for building constructs, aeronautical engineering, *etc.*). Such
29 materials were chosen as long as they were tolerated by the human body and met certain
30 physiological force requirements. Failure of these metals and metal alloys are often due to
31 poor surface properties that result in insufficient bonding with juxtaposed bone. Ceramics
32 have also been proposed to serve as orthopedic implant materials. However, ceramics,
33 although possessing exceptional cytocompatibility properties with bone cells, have

1 experienced little use as single-component orthopaedic implants due to poor mechanical
2 properties (such as low fracture toughness) under physiological loading conditions. When
3 loaded, poor mechanical properties of ceramics often lead to crack initiation and propagation
4 events that necessitate surgical removal of failed implants. Even when used as a coating,
5 ceramics often dissolve or fracture before promotion of new bone growth and, thus, often
6 leave a base metal alloy material which was insufficient to support osseointegration in the
7 first place.

8 As previously mentioned bio-ceramics such as, hydroxylapatite and calcium
9 phosphate are quite brittle, and the failure of fixation between bone and the prosthesis may
10 occur. The ideal thickness for these coatings is approximately 20-70 microns (plasma spray
11 deposition). Newer low temperature deposition techniques have also been developed using
12 organics, calcium, and phosphates, which is known to the art as surface-induced
13 mineralization. These coatings have a reported thickness in the order of 5-10 μm . Although
14 these advanced application methods produce uniform ceramic coatings in the micron to
15 nanometer range they are nevertheless susceptible to interfacial failure and remain very
16 brittle. Newer implant designs have been achieved to combat the physical weaknesses of
17 these bio-ceramic coatings. These design features have been incorporated into high stress
18 implants and allow the bio-ceramic coating to be loaded in compression rather than shear
19 force. Such materials however shield by design pose as interfacial failure points. Either new
20 material formulations which simultaneously possess sufficient surface and mechanical
21 properties or novel techniques are required in order to initially form and maintain adequate
22 bonding amid substrate and surrounding bone throughout a patient's life.

23 Furthermore, several concerns about current coating materials and techniques have
24 been raised and are currently being studied. Noted concerns include bond failure between
25 substrate and coating, leading to loosening of the component and ultimate failure of fixation.
26 This substrate coating failure or wear may also lead to particulate debris which induce an
27 immune inflammatory response cascading to osteolysis.

28 The need for a coating to mimic the physicochemical, mechanical interface, and
29 nanometer geometry found in bone not subject to particulate debris is realized in the present
30 invention. This novel combination of properties is achieved through the binding of three
31 dimensional structurally rigid, 1.5 nm POSS nanostructured chemicals to the surface of
32 prosthetics. Such control is desirable in that it affords rational control over surface design and
33 function. Furthermore, it enhances surface tailorability toward improved biological fixation,

1 and reliability, through the presence of well defined nanotopology. Compatabilization of
2 macroscopic prosthetic surfaces at the nanoscopic level (one billionth of a meter features)
3 with hybrid organic-inorganic nanoscopic cages is desirable as it allows for an increased
4 surface area. An appropriate interfacial relationship provides mechanical stability to the
5 implant *in situ*, minimizing motion-induced damage to surrounding tissues, and is imperative
6 for the clinical success of bone implants, and the incorporation of the nanoagents into the
7 know hierarchy of bone and tissue structures (Table 1).

8 Table 1 lists the size range of hollow POSS cages relative to cell dimensions and
9 tissue structural features. The size of POSS is roughly equivalent to the overall dimensions of
10 diameters for several biomaterials, thus at a nanoscopic level POSS can effectively mimic
11 biological topology and thereby encourage cellular integration in tissue organization and
12 structure.

13 **Table 1.** Relative sizes of POSS, cell types, and tissue structural features

Biomaterial	Diameter
Osteoblast Cells	10000 nm
Liver Cells	4000-8000 nm
Red Blood Cells	760 nm
Collagen Helices	1.5 nm
Blood Capillary Pore	4 - 8 nm
Wood Cell Wall	2.5 nm
Hydroxyapatite Crystallites	5 nm
Octacyclohexyl POSS	1.5 nm

14 This invention describes the use of POSS nanostructured hybrid "organic-inorganic"
15 chemicals as biomaterials. Prior art with nanostructured polyhedral oligomeric
16 silsesquioxanes (POSS and POS and POMS), has reported their utility as corrosion resistant
17 materials (U.S. Patent No. 5,858,544) utility for the control of grain structure and aging
18 characteristics of metallic solder alloys, and use of POSS in personal care and medical
19 material applications (U.S. Publication No. 2004/0120915; U.S. Patent Nos. 6,586,548 and
20 6,653,365). This prior art makes no mention of their application and utility as biomaterials or
21 as interfacial biomimetic constructs to improve cell modulation or physical properties.

22 Nanostructured chemicals and in particular POSS cages are the preferred species for
23 modification of implants (Figure 1). Furthermore, the dispersion of the POSS molecules and

1 their compatibility with implant materials and surrounding tissue is thermodynamically
2 governed by the free energy of mixing equation ($\Delta G = \Delta H - T\Delta S$). The nature of the R group
3 and ability of the reactive groups on the POSS cage to react or interact with polymers and
4 surfaces greatly contributes to a favorable enthalpic (ΔH) term while the entropic term (ΔS)
5 for POSS is highly favorable when the cage size is monoscopic and the corresponding
6 distribution of oligomers is 1.0.

7 SUMMARY OF THE INVENTION

8 The present invention provides a biomaterial comprising of a nanostructured chemical
9 preferably from the group of POSS, POS, POMS of the type and combinations thereof with
10 other nanostructured chemicals, nanoparticles or materials of natural or biological origin.
11 Nanostructured chemicals are preferred for use as biomaterials as they are highly dispersible,
12 have systematically controlled chemistry, surface area, surface volume, topology and
13 selectivity in promoting cellular modulation and properties.

14 A simple example of such a biomaterial is the reaction of a POSS silanol
15 $[(R^1SiO_{1.5})_4(R^1HOSiO_1)_3]_{\Sigma 7}$ (where $R^1 = Ph$) to coat a titanium implant and consequently
16 promote the binding and cellular modulation leading to bone formation. A second simple
17 example is the reaction of the formula $[(R^1SiO_{1.5})_4(R^1HOSiO_1)_3]_{\Sigma 7}$ (where $R^1 = isoOctyl$)
18 with soft tissue to promote binding and cellular modulation leading to formation of soft
19 tissue.

20 BRIEF DESCRIPTION OF THE DRAWINGS

21 FIG. 1 shows a comparison of hollow and structurally rigid POSS nanostructured
22 chemicals.

23 FIG. 2 illustrates multi-length scale reinforcement (nano-macro) provided through
24 POSS-surface modification of nanoscopic and macroscopic surfaces.

25 FIGS. 3A, 3B and 3C illustrate surface area and topological control at the nanoscopic
26 level from nanostructured chemicals as monolayer coatings.

27 FIG. 4 shows volume contribution relative to weight percentage loading from adding a
28 1 nm nanostructured chemical.

29 FIG. 5 illustrates surface area contribution relative to weight percentage loading from
30 adding a 1 nm nanostructured chemical.

FIGS. 6 and 7 illustrate the use of $[(\text{phenylSiO}_{1.5})_4(\text{phenyl}(\text{OH})\text{SiO}_{1.0})_3]_{\Sigma 7}$ to form bone in vitro.

FIG. 8 illustrates the immunohistochemistry of Ti cultured with bone stroma cells.

FIGS. 9A and 9B illustrate the formation of scar tissue treated with nanostructured chemicals.

FIGS. 10A-10K provide examples of nanostructured chemicals suitable for incorporation into biomaterials.

DETAILED DESCRIPTION

Definition Of Formula Representations For Nanostructures

For the purposes of understanding this invention's chemical compositions, the following definitions are made for formula representations of Polyhedral Oligomeric Silsesquioxane (POSS) and Polyhedral Oligomeric Silicate (POS) nanostructures.

Polysilsesquioxanes are materials represented by the formula $[\text{RSiO}_{1.5}]_{\infty}$ where ∞ represents molar degree of polymerization and R = represents an organic substituent (H, siloxy, cyclic or linear aliphatic or aromatic groups that may additionally contain reactive functionalities such as alcohols, esters, amines, ketones, olefins, ethers or halides or which may contain fluorinated groups). Polysilsesquioxanes may be either homoleptic or heteroleptic. Homoleptic systems contain only one type of R group while heteroleptic systems contain more than one type of R group.

POSS and POS nanostructure compositions are represented by the formula:

$[(\text{RSiO}_{1.5})_n]_{\Sigma \#}$ for homoleptic compositions

$[(\text{RSiO}_{1.5})_n(\text{R}'\text{SiO}_{1.5})_m]_{\Sigma \#}$ for heteroleptic compositions (where $\text{R} \neq \text{R}'$)

$[(\text{RSiO}_{1.5})_n(\text{RXSiO}_{1.0})_m]_{\Sigma \#}$ for functionalized heteroleptic compositions (where R groups can be equivalent or in equivalent)

$[(\text{RSiO}_{1.5})_n(\text{RSiO}_{1.0})_m(\text{M})_j]_{\Sigma \#}$ for heterofunctionalized heteroleptic compositions

In all of the above R is the same as defined above and X includes but is not limited to OH, Cl, Br, I, alkoxide (OR), formate (OCH), acetate (OCOR), acid (OCOH), ester (OCOR), peroxide (OOR), amine (NR_2), isocyanate (NCO), sugars, peptides, and biological groups.

The symbol M refers to metallic elements within the composition that include high and low Z metals including s and p block metals, d and f block transition, lanthanide, and actinide

1 metals. In particular, the metals Al, B, Ga, Gd, Ce, W, Ni, Eu, Y, Zn, Mn, Os, Ir, Ta, Cd, Cu,
2 Ag, V, As, Tb, In, Ba, Ti, Sm, Sr, Pb, Lu, Cs, Tl, Te are useful. The symbols m and n refer to
3 the stoichiometry of the composition. The symbol Σ indicates that the composition forms a
4 nanostructure and the symbol # refers to the number of silicon atoms contained within the
5 nanostructure. The value for # is usually the sum of m+n, where n ranges typically from 1 to
6 24 and m ranges typically from 1 to 12. It should be noted that $\Sigma\#$ is not to be confused as a
7 multiplier for determining stoichiometry, as it merely describes the overall nanostructural
8 characteristics of the system (aka cage size).

9 The present invention teaches an improved method of designing the surface topology
10 of biomaterials via the use of hollow and structurally rigid POSS nanostructured chemicals as
11 nanoscopic biomaterials and biomimetic surface modifiers.

12 A key feature of the present invention is the use of the three dimensional rigid POSS
13 cage structures to induce proliferation and differentiation of osteoblastic and fibroblastic cells
14 to the surface of implants. The assembly of POSS cages on or within a substrate surface
15 provides a means to promote select cellular adhesion to the prosthesis and biological fixation
16 of the POSS structure into juxtaposed bone. A range of cage sizes and formula are applicable
17 and include POSS cages containing one or more R groups such as mono through tetra
18 peptides (e.g. RGD, KRSR) which are known to induce bone growth, and R groups such as
19 glycosides and sugars (e.g. triterpene glycosides such as 27-deoxyactein) that are known to
20 promote enzyme activity, and groups such as anti-inflammatory agents (e.g. heparin) and
21 antibacterials (e.g. Ag⁺ cations, linezolid). The composition is not limited to these specific
22 examples but can also contain additional biological factors. Biological factors include, for
23 example, ascorbic acid-2-phosphate, dexamethasone, beta-glycerophosphate and TGF
24 superfamily proteins, such as the bone morphogenic proteins (BMPs). The composition can
25 also contain antibiotic, antimycotic, antiinflammatory, immunosuppressive and other types of
26 therapeutic agents. There is tremendous value in the incorporation of POSS cages bearing
27 mixtures of R groups present on the surface of an implant as it can serve to reduce infection
28 and increase the rate of healing. The useful range of POSS silanol is from 0.01% to 99% on
29 the surface of the implant with a preferred useful range of 0.1% to 10%.

30 The incorporation of POSS provides control over surface area, surface roughness,
31 surface topology, and surface energy.

General Process Variables Applicable To All Processes

As is typical with chemical processes, there are a number of variables that can be used to control the purity, selectivity, rate and mechanism of any process. Variables influencing the process include the size and polydispersity, and composition of the nanostructured chemical, separation and isolation methods, and use of catalyst or cocatalysts, solvents and cosolvents. Additionally, kinetic and thermodynamic means of controlling the adhesion mechanism, rate, and product distribution are also known tools of the trade that can impact product performance, quality and economics.

Example 1.

Coating of $[(\text{RSiO}_{1.5})_4(\text{R}(\text{HO})\text{SiO}_{1.0})_3]_{\Sigma 7}$:

$[(\text{RSiO}_{1.5})_4(\text{R}(\text{OH})\text{SiO}_{1.0})_3]_{\Sigma 7}$ (1 g) was dissolved in dichloromethane and sprayed onto metallic titanium samples. The samples were then dried at 110°C for 2 hours.

Cell Adhesion Findings.

Experimental samples with 50% surface coverage of POSS were exposed to osteoblasts and fibroblasts cultured in Dulbecco's modified eagle medium (DMEM), supplemented with 10% fetal bovine serum (FBS) and 1% penicillin/streptomycin (P/S), under standard cell culture conditions (sterile chamber maintained at 37 °C and a humidified environment: 5% CO₂/95% air). The stock solutions were supplied by HyClone.

For this purpose, osteoblasts, and fibroblasts were separately seeded (10,000 cells cm²) onto the experimental titanium substrate, and were allowed to adhere in standard cell culture conditions for 48 hours. After the prescribed time period, substrates were rinsed three times using phosphate-buffered saline (PBS) to remove non-adherent cells. The adhered cells were fixed with formaldehyde (Fisher), stained with Hoechst 33 258 dye (Sigma), and counted using fluorescence microscopy (365 nm excitation and 400 nm emission wavelengths). The findings in Table 2 indicate a clear differentiation in binding a cellular modulation relative to the type of R group present on the cage. Specifically, osteoblast exhibited a preference for $[(\text{phenylSiO}_{1.5})_4(\text{phenyl}(\text{OH})\text{SiO}_{1.0})_3]_{\Sigma 7}$ while fibroblasts preferred $[(\text{isoOctylSiO}_{1.5})_4(\text{isoOctyl}(\text{OH})\text{SiO}_{1.0})_3]_{\Sigma 7}$.

Table 2. Cellular adhesion measured in cell density / cm²

Sample	Osteoblast Cell Count	Fibroblast Cell Count
wrought titanium control	~1,600/cm-2	~2,500/cm ²
wrought titanium + [(phenylSiO _{1.5}) ₄ (phenyl(OH)SiO _{1.0}) ₃] _{Σ7}	~7,800/cm-2	~3,200/cm ²
wrought titanium + [(isoOctylSiO _{1.5}) ₄ (isoOctyl(OH)SiO _{1.0}) ₃] _{Σ7}	~3,400/cm-2	~6,800/cm ²

All experiments were run in triplicate, and repeated three different times.

Example 2. OsteoPOSS

Figure 6 illustrates the use of [(phenylSiO_{1.5})₄(phenyl(OH)SiO_{1.0})₃]_{Σ7} to form bone in vitro, eight POSS-bone samples 5 mm in length were implanted in vivo into rat calvaria as a bone defect. After one month the bone implantation site was examined and was found to be indistinguishable from normal rat bone. See Figures 7 and 8.

Example 3. FibroPOSS.

Based upon the differentiation from Example 1, a series of in vivo FibroPOSS examinations was made using [(isoOctylSiO_{1.5})₄(isoOctyl(OH)SiO_{1.0})₃]_{Σ7} and [(isoOctylSiO_{1.5})₈]_{Σ8}. In a human arm a series of six cuts were made through the endermal skin layer.

The top two cuts were treated with 100% [(isoOctylSiO_{1.5})₄(isoOctyl(OH)SiO_{1.0})₃]_{Σ7} (SO1455) and [(isoOctylSiO_{1.5})₈]_{Σ8} (MS0805).

The middle two cuts had 50/50 SO1450 + bactin antibiotic and 50/50 MS0805 + bactin antibiotic.

The bottom left cuts had 100% bactin antibiotic and the bottom right cut had no treatment.

All of the cuts healed at the same rate.

The two cuts treated with [(isoOctylSiO_{1.5})₄(isoOctyl(OH)SiO_{1.0})₃]_{Σ7} (SO1455) and [(isoOctylSiO_{1.5})₈]_{Σ8} (MS0805) did not show any bleeding after the POSS was added nor was visible clotting observed. The bottom two cuts did show bleeding and clotting was

evident by scab formation. The $[(\text{isoOctylSiO}_{1.5})_4(\text{isoOctyl}(\text{OH})\text{SiO}_{1.0})_3]_{\Sigma 7}$ (SO1455) and $[(\text{isoOctylSiO}_{1.5})_8]_{\Sigma 8}$ (MS0805) are attributed to having stopped bleeding by plugging the 4-8 nm porosity between the endothelial capillary cells which in turn caused a hydrophobic constriction of the capillary and consequent stoppage of bleeding without clotting.

All of the cuts treated with the POSS formed oriented scar tissue. The formation of oriented scar tissue is evidence of enhanced fibroblast bonding and orientation these cells. See Figure 9.

Example 4. Application to personal care and cosmetics.

In light of the observed cellular differentiation and modulation promoted by nanostructured chemicals, a series of POSS, POS and POMS were added to conventional personal care and cosmetic products. This work was done to demonstrate the ability to add nanostructured chemicals to such products to promote biomimetic activity in such products without altertering their desirable product features, manufacturing methods, or method of application. A summary of the products and finding is listed below. Structure examples are shown in Figures 10A-10K.

Each sample prepared consisted of approximately 5% of POSS by weight and was inspected visually and by biometric techniques for the dispersion of the POSS compound. The products in which the POSS compounds could be dispersed without being felt are listed under the POSS compounds studied.

SO1450

Suave Shampoo, Right Guard Deodorant, Isoplus Styling Gel, Softsoap Bodywash, Clean & Clear Facewash, Nair Hair Remover, Nicel Face Cream, LA Colors Makeup, Hard as Nails Nail Polish, Smackers Lip Gloss.

SO1458

Dial Antibacterial Hand Soap, Suave Shampoo, Aveeno Lotion, Aquaphor Moisturizer, Right Guard Deodorant, Isoplus Styling Gel, Softsoap Bodywash, Clean & Clear Facewash, Nair Hair Remover, Nicel Face Cream, LA Colors Makeup, Hard as Nails Nail Polish (remained clear), Smackers Lip Gloss.

MS0840

Dial Antibacterial Hand Soap, Ivory Hand Soap, Suave Shampoo, Aveeno Lotion, Aquaphor Moisturizer, Right Guard Deodorant, Softsoap Bodywash, Clean & Clear Facewash, Nair Hair Remover, LA Colors Makeup, Hard as Nails Nail Polish, Smackers Lip Gloss.

OL1160

Dial Antibacterial Hand Soap, Ivory Hand Soap, Suave Shampoo, Aveeno Lotion, Aquaphor Moisturizer, Right Guard Deodorant , Softsoap Bodywash, Clean & Clear Facewash, Nair Hair Remover.

OL1170

Nicel Face Cream, LA Colors Makeup, Hard as Nails Nail Polish (remained clear) Smackers Lip Gloss (remained clear).

MS0825

Dial Antibacterial Hand Soap, Ivory Hand Soap, Suave Shampoo, Aveeno Lotion, Aquaphor Moisturizer, Right Guard Deodorant, Softsoap Bodywash, Clean & Clear Facewash, Nair Hair Remover, Nicel Face Cream, LA Colors Makeup, Hard as Nails Nail Polish (remained clear), Smackers Lip Gloss (remained clear).

MS0802

Dial Antibacterial Hand Soap, Ivory Hand Soap, Suave Shampoo, Aveeno Lotion, Aquaphor Moisturizer, Right Guard Deodorant, Softsoap Bodywash, Clean & Clear Facewash, Nair Hair Remover, Nicel Face Cream, LA Colors Makeup.

SO1455

Dial Antibacterial Hand Soap (remained clear), Ivory Hand Soap (remained clear), Suave Shampoo (remained clear), Aveeno Lotion, Aquaphor Moisturizer, Right Guard Deodorant (became thicker), Isoplus Styling Gel (became thicker), Softsoap Bodywash, Clean & Clear Facewash, Nair Hair Remover, Dollar General Astringent, 409 Cleaner, Glass Plus Cleaner , Nicel Face Cream, Smackers Lip Gloss.

1 PM1285

2 Dial Antibacterial Hand Soap (remained clear), Ivory Hand Soap (remained clear),
3 Suave Shampoo (remained clear) Aveeno Lotion, Aquaphor Moisturizer, Right Guard
4 Deodorant, Isoplus Styling, Nair Hair Remover, Nicel Face Cream, Smackers Lip Gloss, Hard
5 as Nails Nail Polish (became thicker).

6 While certain representative embodiments and details have been shown for purposes
7 of illustrating the invention, it will be apparent to those skilled in the art that various changes
8 in the methods and compositions disclosed herein may be made without departing from the
9 scope of the invention which is defined in the claims.

WHAT IS CLAIMED IS:

- 1 1. A method of fabricating a biomaterial comprising incorporating a compound selected
2 from the group consisting of polyhedral oligomeric silsesquioxanes, polyhedral oligomeric
3 silicates, and polyhedral oligomeric metallasesquioxanes into a material that interacts with a
4 biological system.
- 1 2. A method according to claim 1, wherein the compound modifies the hydrophilicity or
2 hydrophobicity of the material.
- 1 3. A method according to claim 1, wherein the compound is used to prepare an implant
2 surface and has a property selected from the group consisting of anti-inflammatory, cell-
3 growth promoter, and antibacterial.
- 1 4. A method according to claim 1, wherein the compound has a plurality of different
2 organic substituent groups.
- 1 5. A method according to claim 1, wherein a plurality of compounds having different
2 organic substituent groups are used.
- 1 6. A method according to claim 1, wherein a plurality of compounds having different
2 cage sizes are used.
- 1 7. A method according to claim 1, wherein the biomaterial is formed by a process
2 selected from the group consisting of melt mixing with polymers, copolymerization, reactive
3 chemical grafting, non-reactive grafting, vapor deposition, and sputtering.
- 1 8. A method according to claim 1, wherein a silanol functional group on the selected
2 compound is reacted with a metal implant.
- 1 9. A method according to claim 8, wherein the compound used to prepare the implant
2 has a property selected from the group consisting of anti-inflammatory, cell growth promoter,
3 and antibacterial.

1 10. A method according to claim 8, wherein the compound has a plurality of different
2 organic substituent groups.

1 11. A method according to claim 8, wherein a plurality of compounds having different
2 organic substituent groups are used.

1 12. A method according to claim 8, wherein a plurality of compounds having different
2 cage sizes are used.

1 13. A method according to claim 1 wherein the compound is incorporated into a material
2 selected from the group consisting of cosmetics, stents, metal prosthetics, plastic prosthetics,
3 bioderived prosthetics, personal care products, drug delivery agents, medical materials,
4 medical sensors, contrast agents, and biomarkers.