Nanotechnology to Benefit Tissue Engineering

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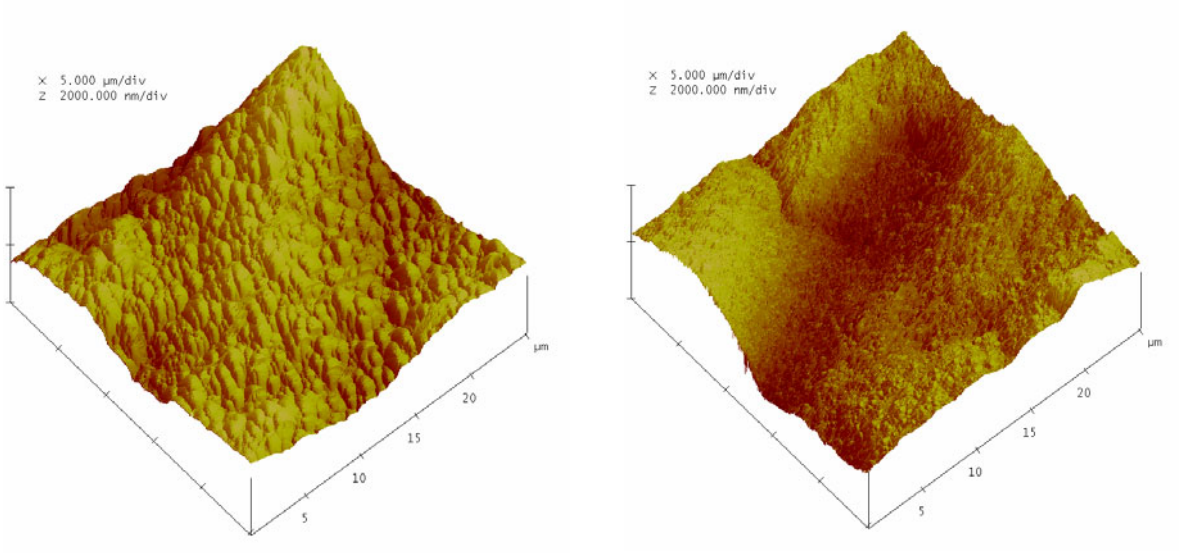
Introduction

Nanobiotechnology is a growing area of research primarily due to the potentially numerous applications of new synthetic nanomaterials in engineering/science. Although various definitions have been given to the word "nanomaterials" by many different experts, the commonly accepted one refers nanomaterials as those materials which possess grains, particles, fibers, or other constituent components that have one dimension specifically less than 100 nm [1-26] (Figure 1). For example, in catalytic applications, compared to conventional grain size (or greater than 1 μm) magnesium oxide, nanophase grain size magnesium oxide adsorbed up to ten times more organophosphorous and chlorocarbons [27]. It was speculated that nanophase compared to conventional grain size magnesium oxide increased adsorption of these species due to greater numbers of atoms at the surface, a higher surface area, increased grain boundaries at the surface, and less acidic OH- groups (due to a much larger proportion of edge sites for the nanophase magnesium oxide to cause delocalization of electrons; Figure 1) [27].



(a) Conventional or micron grain material

(b) Nanophase or nanometer grain material

Figure 1: Difference in surface properties of conventional compared to nanophase alumina. AFM scan size = 25 by 25 μm. For the nanophase material (b), note the smaller particles, increased nanometer surface roughness, and increased grain boundaries (or defects) at the surfaces.

Such novel surface properties important for catalytic applications have been implemented into tissue engineering applications. Specifically, nanophase ceramics, metals, polymers, and composites thereof have been investigated for orthopedic (Table 1), vascular (Table 2), cartilage (Table 2), bladder (Table 2), and central/peripheral nerve (Table 3) applications. Importantly, for all materials and all applications, in vitro data suggests that compared to respective conventional materials, nanophase materials increase tissue growth.

This has been attributed to the noted increased surface reactivity of nanophase compared to conventional materials [1-27].

Table 1: Nanophase Materials in Orthopedics

Reference	Application	Cell	Altered Function	Nanophase Material
Webster et al. [1-10]	Orthopedic	Osteoblast Osteoclast Fibroblast	Increased adhesion, proliferation, and synthesis of extracellular matrix Increased formation of resorption pits and synthesis of TRAP Decreased adhesion	Alumina, titania, and hydroxyapatite with grain sizes less than 67 nm
Ejiofor et al. [11]	Orthopedic	Osteoblast	Increased adhesion and proliferation	Titanium, Ti6Al4V, CoCrMo with nanostructured surface features
Price et al. [12]; **Elias et al. [13]**	Orthopedic	Osteoblast Fibroblast	Increased adhesion, proliferation, and synthesis of extracellular matrix Decreased adhesion	Single phase carbon and alumina fibers less than 100 nm in diameter and in a polymer composite
McManus et al. [14]; **Kay et al. [15]**	Orthopedic	Osteoblast	Increased adhesion, proliferation, and synthesis of extracellular matrix	Alumina, titania, and hydroxyapatite with grain sizes less than 67 nm in a polymer composite
Supronowicz et al. [16]	Orthopedic	Osteoblast	Increased adhesion, proliferation, and synthesis of extracellular matrix	Carbon nanotubes under an electrical stimulus
Zhang et al. [17]; **Kay et al. [15]**	Orthopedic	Osteoblast	Increased adhesion, proliferation, and synthesis of extracellular matrix	Polymers with nanostructured surface features

Table 2: Nanophase Materials in Bladder, Vascular, and Cartilage Applications

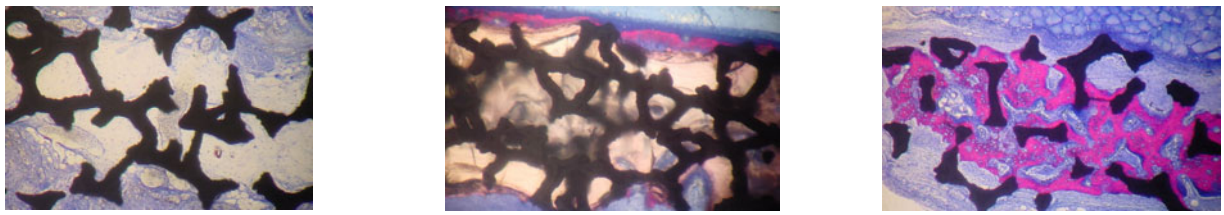
Reference	Tissue Engineering Application	Cell	Altered Function	Nanophase Material
Thapa et al. [18]	Bladder	Smooth muscle cells	Increased adhesion and proliferation	Polymers with nanostructured surface features
Miller et al. [19]	Vascular	Smooth muscle cells Endothelial cells	Increased adhesion and proliferation Increased adhesion and proliferation	Polymers with nanostructured surface features
Park et al. [20]	Cartilage	Chondrocytes	Increased adhesion and proliferation	Polymers with nanostructured surface features
Savaiano et al. [21]	Cartilage	Chondrocytes	Increased adhesion, proliferation, and synthesis of an extracellular matrix	Alumina, titania, and hydroxyapatite with grain sizes less than 67 nm in a polymer composite
Dalby et al. [22]	Vascular	Endothelial cells	Increased spreading	13, 35, and 95 nm islands created by polymer demixing

Table 3: Nanophase Materials in Central/Peripheral Nervous System Applications

Reference	Tissue Engineering Application	Cell	Altered Function	Nanophase Material
McKenzie et al. [23]	Neural	Neurons Astrocytes	Increased formation of neurites Decreased adhesion and proliferation	Single phase carbon fibers less than 100 nm in diameter and in a polymer composite
Mattson et al. [24]	Neural	Neurons	Increased axonal extension	Carbon nanotubes chemically-functionalized
Turner et al. [25]	Neural	Neurons	Increased axonal extension	Silicon with nanostructured columns
Torimitsu et al. [26]	Neural	Neurons	Increased axonal outgrowth	Nanostructured silicon

Increased in vivo Response of Nanomaterials

While most of the evidence for the use of nanomaterials in tissue engineering applications includes in vitro analyses, there are some limited studies highlighting successful in vivo regeneration of tissues (Figure 2). For example, tantalum scaffolds were coated with nanometer compared to conventional hydroxyapatite particles, implanted into the calvaria of rats, and new bone measured through histology stains [28]. Results provided some of the first evidence highlighting increased bone infiltration into the tantalum scaffold coated with nanophase hydroxyapatite after 6 weeks. In contrast, no bone infiltration was observed for uncoated tantalum scaffolds or those coated with conventional grain size hydroxyapatite. In this manner, the promising in vitro results of greater tissue regeneration on nanophase compared to conventional materials translates in vivo.



(a) Uncoated tantalum scaffolds **(b) Tantalum scaffolds coated with conventional HA** **(c) Tantalum scaffolds coated with nanophase HA**

Figure 2: Increased Bone Ingrowth for Tantalum Scaffolds Coated with Nanophase Hydroxyapatite (c) After 6 Weeks Implantation Into Rat Calvaria.
Stain = blue mineralized bone and red unmineralized bone.

Discussion and Conclusions

Mammalian cells have shown a definite positive response to nanophase materials for orthopedic, vascular, cartilage, bladder, and central/peripheral nervous systems. The theory behind the success of nanophase materials for tissue engineering applications, relies on the fact that surface properties (such as area, charge, and topography) depend on the grain size and subsequent changes in surface features of a material. In this respect, nanophase materials that, by their very nature, possess greater numbers of atoms at the surface, higher surface areas, larger portions of surface defects (such as edge/corner sites), increased electron delocalization, and greater numbers of grain boundaries at the surface have an advantage over conventional larger grain size materials for many biological applications. All of these factors contribute to higher surface reactivity of nanophase compared to conventional materials. Thus, it is reasonable to speculate why initial protein interactions responsible for subsequent increased tissue growth on nanophase compared to conventional materials would be enhanced. Specifically, mammalian cell-adhesive epitopes in vitronectin (for example, Arginine-Glycine-Aspartic acid or RGD) were exposed to a greater extent when adsorbed on nanophase compared to conventional alumina surfaces [8]. While a number of investigators have demonstrated increased tissue growth on nanophase materials, how such novel nanophase materials will be incorporated into the next-generation more effective biomaterials remains to be seen.

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