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Trends in nanotechnology towards the diagnosis and cure of arthritis

Lekshmi Gangadhar[1], P.K.Praseetha[2*], Murthy S.Chavali[3]

[1]Department of Nanotechnology, Noorul Islam Centre for Higher Education, Kumaracoil, Tamil Nadu, (INDIA)

[2]Corresponding author- Department of Nanotechnology, Noorul Islam Centre for Higher Education, Kumaracoil, Tamil Nadu, (INDIA)

[3]Department of Nanotechnology, Noorul Islam Centre for Higher Education, Kumaracoil, Tamil Nadu, (INDIA)

E-mail : crkpkp@gmail.com

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ABSTRACT

In recent years, nanotechnology has developed to a stage that makes it possible to produce, characterize and specifically tailor the structural and functional properties of nanoparticles for clinical applications. Cartilage damage is typically associated with work and athletic injuries, and commonly occurs in conjunction with ACL tears and other ligament problems. Cartilage does not grow back, so treatments to regenerate the tissue are critical. The new biomedical therapy involving nanotechnology promotes the growth of new, stronger cartilage to aid in the treatment of joint injuries. This review article analyses the various technologies available for the diagnostic and therapeutic potentials of nanotechnology towards chronic arthritis.

KEYWORDS

Osteoarthritis;
Cartilage;
Nanotechnology;
Treatments.

INTRODUCTION

One of the potential applications of nanotechnology is that it provides promising improvements in the medical field. The ultimate promise of nanomedicine is the eradication of disease. To accomplish this goal, convergence of nanotechnology and biotechnology along with biomedical principles is required. Nanotechnology provides a wide range of new technologies that optimize the uptake and delivery of pharmaceutical products. Drugs need to be protected during their transit to the target area in the body while maintaining their biological and chemical integrity. Osteoarthritis, a degenerative joint disease prevalent among older people, starts at the molecular scale and progressively spreads to the higher architecture of the cartilage mesh. Pain is caused by wearing down of the cartilage that cushions joints, and a decrease in the fluid that keeps them lubricated. Nanotechnology provides a new generation of biocompatible nanomaterials for repairing and replacing human tissues. Nanotechnology provides a new generation of biocompatible nanomaterials for repairing and replacing human tissues and opts for alternative medical therapies.

SEVERITY OF THE DISEASE

Osteoarthritis is a disease of the joints. Unlike many other forms of arthritis that are systemic illnesses, such as rheumatoid arthritis and systemic lupus, osteoarthri-

tis does not affect other organs of the body[1, 2]. The most common symptom of osteoarthritis is pain in the affected joints after repetitive use. There can be swelling, warmth, and creaking of the affected joints[3]. Pain and stiffness of the joints can also occur after long periods of inactivity. In severe osteoarthritis, complete loss of the cartilage cushion causes friction between bones, causing pain at rest or pain with limited motion[4]. Symptoms of osteoarthritis vary greatly from patient to patient[5]. Some patients can be debilitated by their symptoms. On the other hand, others may have remarkably few symptoms in spite of dramatic degeneration of the joints apparent on X-rays.

DIAGNOSIS OF OSTEOARTHRITIS

Blood tests can only be performed to exclude diseases that can cause secondary osteoarthritis, as well as to exclude other arthritis conditions that can mimic osteoarthritis. X-rays of the affected joints can suggest on osteoarthritis. The common X-ray findings of osteoarthritis include loss of joint cartilage, narrowing of the joint space between adjacent bones, and formation of bone spur. Simple X-ray testing can be very helpful to exclude other causes of pain in a particular joint as well as assist in decision making as to when surgical intervention should be considered[6].

Arthrocentesis is a procedure where a sterile needle is used to remove joint fluid for analysis. Joint fluid analysis is useful in excluding gout, infection, and other causes of arthritis. A careful analysis of the location, duration, and character of the joint symptoms and the appearance of the joints helps the doctor in diagnosing osteoarthritis. Bony enlargement of the joints from spur formations is characteristic of osteoarthritis. Therefore the presence of Heberden's nodes, Bouchard's nodes, and bunions of the feet can indicate the diagnosis of osteoarthritis.

CAUSES OF OSTEOARTHRITIS

The cause may be endocrinal when people with diabetes are prone to osteoarthritis. Others like acromegaly, hypothyroidism, hyperthyroidism, hyperparathyroidism and obesity also may be the reasons. Macrotrauma or microtrauma can lead to the severity in case of post traumatic cases which leads to a damged cartilage[6]. Chronic gouty arthritis and rheumatoid diseases may lead to the anomaly in case of inflammatory joint disease. Metabolic variations including Pagets and Wilson diseases can lead to the occurrence. When the cause is genetic, breakage of cartilage and collagen disturbance may result due to Ehlers- Danlos syndrome. Neuropathic defects may affect the loss of sensation along with nerve problems. Hemophilia and sickle cell disease can form one of the major reasons for the osteoarthritis in combination with nutritional defects.

EXISTING CURE

Dietary recommendations to cure arthritis

Potato Juice, Green Leafy Vegetable Juice, Pineapple Juice, Sesame Seeds, Copper, Calcium, Garlic, Banana, Lime, Alfalfa, Green Gram and castor Oil are the traditionally available food ingredients to be added for the patients[7]. Supplements such as glucosamine sulfate and chondroitin sulfate are widely used but not regulated by the FDA. Glucosamine, an amino monosaccharide, is a primary component of connective tissue[8]. Chondroitin sulfate is found in proteoglycans which contribute to the stability of cartilage. In supplementation form, chondroitin is derived from bovine and calf cartilage. An arthritis patient has a supplement in addition to the daily food with nanosilica under the commercial name dynamsi which is a purely natural food supplement with the detoxicating characteristics of Silica. A calcium supplement to the Nano Silica (DynamSi) is also recommended.

Surgical treatment options

a) Chondroplasty

In addition to nonsurgical management of osteoarthritis, several surgical options exist. Surgical options include first a knee arthroscopy and chondroplasty. Chondroplasty is a smoothing of roughened articulate cartilage. The smoothing may decrease the friction inside the joint but is performed conservatively as to prevent thinning of the surface cartilage.

b) Abrasion/ Microfracture

Abrasion arthroplasty, or micro-fracture, is appropriate for small areas of exposed bone or complete loss

of cartilage[9, 10]. Abrasion of the area of exposed bone is performed with a surgical procedure which stimulates the bone to bleed allowing the bone to grow the scar cartilage over the previously exposed area. The resulting cartilage growth and its effectiveness are variable between patients.

c) Arthroscopy

Arthroscopy is a surgical technique whereby a a viewing tube is inserted into the joint space[11]. Abnormalities of and damage to the cartilage and ligaments can be detected and repaired through the arthroscope. Patient's recovery from the arthroscopic surgery is much quicker than from open joint surgery.

d) OATS Procedure

Osteochondral Autograft (or allograft) transplant (OATS procedure) can be performed for small to moderately large area of full thickness surface cartilage loss. These areas of full thickness cartilage loss are also referred to as grade IV chondromalacia. This procedure involves first removing a cylinder shaped bone which is lacking surface cartilage and replacing it with a dowel or cylinder of bone with intact surface or articulate cartilage. The replacement dowel of bone with surface cartilage can either come from a non weight bearing area of bone and surface cartilage from the knee (AUTOGRAFT) or from a cadaver (ALLOGRAFT).

e) Meniscus transplant

Meniscal transplant involves implanting either a medial or lateral meniscus from a cadaver into a knee joint that is lacking greater than 50% of meniscal cartilage. X-rays or an MRI are used to measure the patient's knee to determine the dimensions of the meniscus needed. This procedure however, has only been found to be useful in patients with intact surface cartilage above and below the meniscus.

f) Osteotomy of tibia and femor

An Osteotomy is a realignment procedure that unloads the vulnerable or arthritic side of the knee and puts the majority of the load of the knee joint onto the underutilized cartilage on the other side of the knee.

g) Unicompartmental knee replacement

Another option for patients with osteoarthritis in one area of the knee- usually medial or lateral is an artificial resurfacing of the cartilage surface, called a unicompartmental knee replacement. This procedure is successful in relieving symptoms from osteoarthritis if the arthritis is limited to one compartment or area of the knee.

h) Artificial joint resurfacing or total knee replacement

Artificial joint resurfacing involves caping the end of the femur (thigh bone) and tibia (shin bone) with plastic and or metal pieces[12]. These pieces are glued in place to form an artificial joint surface. This procedure can be very effective in eliminating painful and severe Osteoarthritis, but it is limited by the fact that the articular components (plastic and metal) will eventually wear out and need to be replaced[13]. Biologic living joints can live for 60-80 years which cannot be done by artificial joints.

Nonsurgical treatment options

a) Exercise and weight loss

Nonsurgical management starts with weight loss and muscle strengthening. Each pound of weight can put up to 6 pounds worth of pressure on the knee joint during activity. Thus people of a larger size tend to develop arthritis at an earlier age and to a greater severity than their slim counterparts[14]. Muscle strength is also vital in combating osteoarthritis. The muscles surrounding the knee joint act as shock absorbers for the pressure that daily activities and sports place on the joint. Increasing muscle strength will decrease pressure otherwise placed on the joint, thus decreasing symptoms.

b) Bracing

Knee braces are available for treatment of medial compartmental osteoarthritis (arthritis on the inside of the knee joint). These braces work by unloading the medial (inside) portion of the knee.

c) Medications

In addition to weight loss and strengthening, anti-inflammatory medications may also help decrease symptoms[15, 16]. Aspirin, Ibuprofen (Advil) and Naprosyn (Aleve) are all examples of over the counter anti-inflammatory medications (NSAIDs). Other prescription strength NSAIDs includes Indocin, Daypro, Relafen, Celebrex, Lodine, and Mobic. Acetaminophen (Tylenol)

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may also be taken for pain but it is less effective for inflammation than other medications. Penetrating Heat Therapy Cream is a Capsaicin-based cream that is especially effective for arthritis and deep muscle pain. Capsaicin has been scientifically and clinically shown to gradually deplete Substance P, the chemical in the body that creates the sensation of localized pain. In addition to the Capsaicin-based formula, a Menthol and Camphor-based formula was developed with two different application methods: a Triple Strength Pain Relief Rub and a Targeted Relief Spray. The nano-encapsulated spray is useful for pain sufferers who are unable to reach painful areas such as their back or feet or for untouchable gout pain areas[17]. The MyOmega formula includes Omegas 3, 6 and 9, derived from the Brazilian Açai bery, which provide a silky, luxurious feel and a high level of antioxidants.

e) Viscosupplementation

Within the knee joint synovial fluid is highly viscous which provides a friction-free environment. Hyaluronic acid (HA) which is present in our synovial fluid is also found in most body tissues[18]. In a healthy adult, synovial fluid HA has a molecular weight of 4-5 million. As a result of this large size HA molecules entangle, forming coiled configurations which in turn provide elasticity and viscosity to synovial fluid. HA also binds to proteoglycans to stabilize the structure of the articulate cartilage[19]. In patients with OA, the molecular weight of the HA decreases causing the synovial fluid to become less viscous thus leading to increased friction and abnormal joint movement. Lubrication or Hylagan injections provide the joint extra lubrication and shock absorption, as well as decrease friction or rubbing within the joint which may slow the progression of osteoarthritis[20].

f) Cortisone injection

Injection of cortisone into the knee joint has been shown to be effective for 'flares' of arthritis symptoms, as they are a direct acting anti-inflammatory medication. However, research has also shown deterioration of articulate cartilage after repeated cortisone injections.

Implications of nanotechnology in the treatment of arthritis

The fascinating and versatile toolbox offered by nanotechnology is about to find a prime application in life sciences[21, 22]. Nanotechnology will advance today's medicine in two ways: First by improving current technology and secondly by offering new bio and nanomaterials. This will probably be the main impact in medicine in the short term. Pathological situations such as acute trauma or chronic inflammation may lead to the degradation of the articulating surfaces in the affected joints[23, 24]. Unlike bone, cartilage does not grow back. So treatments to regenerate the tissue are critical. Current cartilage repair techniques often lead to Type I collagen, which resembles scar tissue but the normal cartilage is composed of Type II collagen. The self-assembling peptide molecules are able to more closely mimic the nano-structure of natural cartilage[25].

Diagnostic procedures at nanoscale

a) Quantum dots and nanospheres

The diagnosis of Osteoarthritis could be made easier by the quantum dots that could play a part in the diagnosis of kidney failure, as they clump around damaged tissue, which in this case would be the cartilage or inflammation of tissues surrounding the cartilage. This has provided the information that they would possibly be able to use further discoveries from nanotechnology to help ease the problem[26]. The treatment of Arthritis involves mainly medicines, physiotherapy and, in severe cases, surgery. Nanotechnology could aid the ingestion of medicines, and possibly the surgery aspect of this treatment. As before, the slow release mechanism found in nanospheres could be used to give patients their analgesics, anti-inflammatory drugs and biologic response modifiers[27]. As patients are generally required to take these drugs for a long period of time, it would be easier for them if a microchip was installed, as this would provide a constant supply of the drugs instead of large doses at intervals. The use of nanospheres would also prevent stomach problems that can occur from the oral ingestion of these medicines, as the drugs would be released directly into the bloodstream and would not have to go via the oral route. Severe arthritis often results in surgery for a variety of operations, one being the repair of damaged tendons. Using the idea of the scaffolds designed, a less intrusive surgery could be introduced, with the regeneration of tissue instead of the traditional scalpel method. This would reduce the trauma to the

surrounding tissue whilst still being as effective as the manual procedure.

b) Biosensor based methods

A facile and label-free biosensing method[28, 29] has been developed for determining osteoarthritis concerned cytokine, interleukin-1 beta (IL-beta), in synovial fluids. The biosensing technique, fiber-optic particle plasmon resonance (FOPPR), is based on gold nanoparticles-modified optical fiber where the gold nanoparticle surface has been modified by a mixed self-assembled monolayer for further conjugation of anti-IL-1 beta antibody and minimization of nonspecific adsorption. Upon binding of IL-1 beta to anti-IL-1 beta on the gold nanoparticle surface, the absorbance of the gold nanoparticle layer on the optical fiber changes and the signal change is enhanced through multiple total internal reflections along the optical fiber. The detection of IL-1 beta in synovial fluid by this sensor agrees quantitatively with the clinically accepted enzyme-linked immunosorbent assay (ELISA) method but a much shorter analysis time is required (<10 min). Such a sensor represents a major advancement in the field of real-time monitoring of low molecular weight proteins in complex biological fluids. The fusion of nanobiosensors and nanofluidics could allow the exploration of candidate drug and target interactions at the single molecule level.

c) Atomic force microscopy

The pathological changes in osteoarthritis start at the molecular scale and spread to the higher levels of the tissue architecture[30, 31]. Nanoscale AFM detects diseases inflicting hierarchically organized tissues at the molecular scale where they begin which enables orthopaedic surgeons to make an early diagnosis and treatment of cartilage diseases in the knee or hip joints. AFM may be employed for diagnostics & to develop drugs and treatments[32, 33].

Cure

a) Magnetic particles

Guiding drug-loaded magnetic particles using a magnet outside the body is not a new idea[34]. If a drug can be guided to the right place in the body, the treatment is more effective and there are fewer side-effects. With the help of nanotechnology, magnetic nanoparticles were developed that can be directed to metallic implants such as artificial knee joints, hip joints and stents in the coronary arteries[35, 36]. By attaching a clot-dissolving drug to the nanoparticles and with the help of magnets the particles were directed to a blood clot in a stent in the heart to dissolve it. Thus the nanoparticles have been able to stop an incipient heart attack. They could also carry antibiotics to treat an infection developed after insertion of an implant.

b) Nanospheres

Each nanosphere within the Icepearls system has a designed-in release time. Some nanospheres are activated immediately when a MyOmega 3 cream, rub or spray is applied to a target pain area, releasing a complex of pain relief ingredients[37, 38]. Other nanospheres are encapsulated within microspheres which have individualized release barriers of varying thicknesses. When the time-based barriers dissolve, new pain relief ingredients are released to the target pain area. The process is continual and fully effective for up to 6 hours. Also nanosphere use nanoparticles of gold that are decorated with oligonucleotides. These are used as probes for the detection of Single Nucleotide Polymorphisms. These include silver deposition onto bound gold particle (to amplify the detection signal) and a colorimetric test (Spot Test) where the nanoparticle is coloured red when in solution, but changes to blue when it binds complementary DNA[39].

c) Co-ordinated molecular therapy

Researchers aim at inducing the self healing capacity of damaged cartilage and bone by coordinated cooperation/ interaction of gene vectors, mesenchymal stem cells, polymers and magnetic nanoparticles[40]. Now, use of biocompatible magnetic nanoparticles and the development of gene vectors supplying cells with genes for therapeutic purposes have come up. By being able to specifically switch on and off gene vector activity and embedding of vectors and cells in synthetic hyaluronic acid gels and bone substitute materials which leads the limiting of gene vector action to the diseased tissue. In this manner e.g. magnetic nanoparticles warm up, when placed in a magnetic field, which in turn leads to activation of a heat shock (HSP70) gene switch that regulates production of BMP-2. At the same time the synthetic hyaluronic acid gel in which the stem cells are

embedded will shrink leading to increased release of Transforming Growth Factor beta (TGFß) gene vector.

d) Liposome injections

Injections of tiny globules of fat using nanotechnology have been proposed by researchers to treat the degenerative disease osteoarthritis, the erosion of cartilage in the joints. The liposomes with large and small pieces of bone and cartilage facing each other are paired in a physiological liquid in which nanolipids float[41]. The pieces are circulated under pressure as a model of how hip joints move. Thus they were able to test the efficacy of the fatty globules in minimizing friction and erosion of the cartilage and bones. Tests showed that the pace of erosion decreased by 40 percent when liposomes were added to hyaluronic acid compared to hyaluronic acid alone.

e) Nanopatterned biomaterials

Polymer scaffolds

Nanopatterned polymer scaffolds, mimicks the natural way minerals are arranged, are being used to make teeth and bone implants[42]. The same property could be employed for building up a new cartilage implant. Nanopatterning can also be used to place cells in particular locations on the scaffold. In doing so, this could create channels to help nutrient exchange within the new tissue. Nanostructuring the metal surfaces of implants allows better cell attachment - greater than 90% attachment, compared to approximately 50% on regular surfaces. Researchers have developed self-assembling nanotubes as a nanopatterned coating for titanium implants. DNA chemistry is used to form 33 rosette-shaped rings, which then combine to form tubes of 3.5 nanometres width[43].

Titanium nanostructures

Adhesion of bone cells for culture can be favoured by coating nanotitanium. When titanium was coated with the nanotubes, with nanostructuring the metal surface - cell adhesion was increased by approximately one third. Further research has shown that by aligning the nanotubes in the same direction, cell adhesion can be doubled, so that 80% of cells are adhered. The advantage of using nanotubes over other methods is that signalling molecules or amino acids sequences can be attached to the nanotubes. By using sequences specific to a certain tissue type, depending on the implant/scaffold location, cell attachment could be increased even further. Significantly improved osteoblast adhesion has been observed on helical rosette nanotubes regardless of whether they are incorporated into hydrogels or coated on titanium[44, 45]. Increased chondrocyte adhesion was also observed on anodized nanotubular Ti compared to unanodized Ti in a recent study, thus, suggesting the possibility of promoting cartilage growth on anodized Ti.

Tantala

Tantala are used as drug delivery carriers and bioreactors. In addition, hydroxyl groups present on the surface of these nanostructures provide an ideal anchorage for covalent bonding of specific ligands (e.g., streptavidin, antibodies, etc.) Moreover, these nanostructured materials are very promising for applications in catalysis because they enable a fine dispersion and stabilization of small nanoparticles and provide access to a larger number of active sites than the corresponding bulk components. There are several studies with different animal model for in vivo evaluation of tantalum implants in different applications[46, 47]. These components are now being used in the more difficult revision cases with severe bone loss. The porous tantalum revision shell has been used as an ''internalplate'', functioning to compressor distract the pelvic discontinuity depending on the chronicity and healing potential of the fracture. Porous tantalum revision shells and custom components can be used in place of triflange components, acetabular transplant, and cage reconstructions.

Long-term follow-up and comparison with alternative reconstructive techniques will be required to evaluate the true effectiveness of this treatment approach. Nanotechnology has produced novel materials such as nanotubes and nanospheres that feature amazing mechanical properties. Greater amounts of new bone formation occur in the rat calvaria when implanting nanocrystalline Hydroxy Apatite coated tantalum than uncoated and conventional HA coated tantalum. A nano-coated titanium or tantalum implant will therefore be better adapted to the human body and less likely to need to be subsequently removed and replaced by a

new implant[48-50].

f) Growth of the cells in nanolayers- fibres and scaffolds

Cartilage tissue engineering has also benefited from nanostructured self-assembled chemistries[51-53]. A self-assembling peptide (the peptide KLD-12, Lys-Leu-Asp) hydrogel was designed for cartilage repair. For cartilage applications, there has been great interest in incorporating chondrocytes or progenitor cells (such as stem cells) into the 3-D polymer or composite scaffolds during electrospinning. The differentiation of the stem cells into chondrocytes in the nanofibrous scaffold was comparable to an established cell pellet culture[54, 55]. However, the easily fabricated and modified nanofibers possessed much better mechanical properties to overcome the disadvantages of using cell pellets and, thus, were presented as ideal candidates for stem cell transplantation during clinical cartilage repair[56].

The nanofibrous fibrin-based composites promoted osteoblast alkaline phosphatase activity as well as osteoblast marker gene (mRNA) expression to support bone maturation both in vitro and in vivo in a mouse calvarial defect model[57-59]. Alumina nanometer fibers (2– 4 nm > 50 nm), significantly stimulated osteoblast responses such as adhesion, alkaline phosphatase activity, and calcium deposition, when compared with conventional grain size alumina[60]. Importantly, this study also demonstrated increased osteoblast functions on alumina nanofibers compared with alumina nanospheres (23 nm in diameter). It was hypothesized that since alumina nanofibers are more structurally similar to that of calcium phosphate crystals and collagen fibers found in natural bone, another key parameter to emulate in nanostructures for bone replacements is its constituent fibrous nature.

CONCLUSION

It is evident that nanomaterials will eventually improve the design and properties of implants with optimum mechanical strength and durability. The application can spread to the development of artificial heart valves and weight-bearing artificial hip and knee prostheses. Presently, nanostructured surfaces represent a very active field of research and development which may ultimately lead to improved biocompatibility of nanomaterials. The traditional disciplines of biology, engineering and microelectronics are fusing and moving to the nanoscale, to provide systems that can identify and characterise disease and provide solutions based on an individual's unique genotype. Nanotechnology is having a major influence in tissue engineering. By using nanotechnologies to engineer more biocompatible materials that more closely resemble those found in the organ are being modeled. If everything runs smoothly, nanotechnology will one day become part of our everyday life and will help save many lives.

REFERENCES

[1] C.G.Armstrong, V.C.Mow; J.Bone Joint Surg.Am., **64**, 88-94 **(1982)**.
[2] F.C.Arnett, S.M.Edworthy, D.A.Bloch, D.J.McShane, J.F.Fries, N.S.Cooper; Arthritis Rheum., **3**, 315-324 **(1988)**.
[3] Kevin W.Chen, Tianjun Liu; Medical Paradigm., **1**, 36-48 **(2004)**.
[4] G.W.Bourne; The Biochemistry and Physiology of Bone, New York, NY: Academic Press, **(1972)**.
[5] R.Altman, G.Alarcon, D.Appelrouth, D.Bloch, D.Borenstein, K.Brandt; Arthritis Rheum., **34**, 1569-1575 **(1991)**.
[6] G.R.Mundy; Nat.Rev.Cancer., **2**, 584-593 **(2002)**.
[7] S.D.Boden; Clin.Orthop.Relat.Res., **367**, 84-94 **(1999)**.
[8] N.P.Cohen, R.J.Foster, V.C.Mow; J.Orthop.Sports Phys.Ther., **28**, 203-215 **(1998)**.
[9] K.Bargiotas, M.Konstantinos, T.Karachalios, M.Hantes, S.E.Varitimidis; Total Hip Arthroplasty Using Trabecular Metal Acetabular Component, Middle Term Results, 72nd AAOS Annual Meeting, Washington, DC, **27**, 4671-4681 **(2006)**.
[10] A.E.Gross, S.B.Goodman; J.Arthroplasty., **20**, 91-93 **(2005)**.
[11] A.Chandola, Y.Young, J.McAlister, J.S.Axford; J.R.Soc.Med., **92**, 13-16 **(1999)**.
[12] D.S.Garbuz; Oper.Tech.Orthop., **14**, 117-120 **(2004)**.
[13] K.Mustafa, A.Oden, K.Hultenby, K.Arvidson; Biomaterials., **26**, 373-381 **(2005)**.
[14] A.M.Parfitt; Introduction and Overview, Bone, **14**, 435-441 **(1993)**.
[15] P.A.Simkin; J.Rheumatol., **27**, 567-568 **(2007)**.

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[16] S.M.Sporer, M.O'Rourke, W.G.Paprosky; J.Arthroplasty., **20**, 79-84 **(2005)**.
[17] M.Scherge, S.Gorb; In: P.Avouris, K.Von Klitzing, R.Weisendanger; Biological Micro- and Nano-Tribology: Nature's Solutions, 1st Edtition, Berlin: Springer, 304 **(2001)**.
[18] F.Rainer, H.Katzer, V.Ribitsch; Acta.Med.Austriaca., **23**, 133-136 **(1996)**.
[19] J.Y.Kang, C.W.Chung, J.H.Sung, B.S.Park, J.Y.Choi, S.J.Lee, B.C.Choi, C.K.Shim, S.J.Chung, D.D.Kim; Int.J.Pharm., **369**, 114-120 **(2009)**.
[20] E.Ernst; Baillieres Best Pract.Res.Clin.Rheumatol., **14**, 731-749 **(2000)**.
[21] Lijie Zhang, Thomas J.Webster; Nano Today, **4**, 66-80 **(2009)**.
[22] Couillard, Lauren, Safety, Health Research on Nanotechnology Said to Need At Least $100 Million Per Year, Daily Environment Report, **223**, A-5 **(2005)**.
[23] Y.W.Chun, T.J.Webster; Ann.Biomed.Eng., **37**, 2034-2047 **(2009)**.
[24] D.Bruce, Ethical and Social Issues in Nanobiotechnologies, EMBO Reports, **7**, 754-758 **(2006)**.
[25] M.H.A.Hassan; Small Things and Big Changes in the Developing World, Science, **39**, 65 **(2005)**.
[26] D.Wang, F.Caruso; React.Chem.Mater., **14**, 1909-1913 **(2002)**.
[27] C.Berkland, M.King, A.Cox, K.Kim, D.W.Pack; J.Control., **82**, 137-147 **(2002)**.
[28] A.Li, X.Yang, F.Yang, Y.Ma; Biosensors and Bioelectronics, **22**, 1716-1722 **(2007)**.
[29] M.Janders, U.Egert, M.Stelzle, W.Nisch; 18th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Bridging Disciplines for Biomedicine, (Amsterdam), Novel Thin Film Titanium Nitride Micro-Electrodes with Excellent Charge Transfer Capability for Cell Stimulation and Sensing Applications, **245**, **(1997)**.
[30] C.Goldsbury, J.Kistler, U.Aebi, T.Arvinte, G.J.Cooper; J.Mol.Biol., **285**, 33-39 **(1999)**.
[31] D.Stoffler, K.N.Goldie, B.Feja, U.Aebi; J.Mol.Biol., **287**, 741-752 **(1999)**.
[32] M.Stolz, R.Gottardi, R.Raiteri, S.Miot, I.Martin, R.Imer, U.Staufer, A.Raducanu, M.Duggelin, W.Baschong, A.U.Daniels, N.F.Friederich, A.Aszodi, U.Aebi; Nature Nanotech., **4**, 186-192 **(2009)**.
[33] T.Reichlin, A.Wild, M.Durrenberger, A.U.Daniels, U.Aebi, P.R.Hunziker, M.Stolz; J.Struct.Biol., **1521**, 52-63 **(2005)**.
[34] J.Dobson; J.Phys.D.Appl.Phys., **36**, 167-181 **(2003)**.
[35] P.Mequita, R.Branco, A.Afonso; J.Biomed.Mater., **254**, 1091-1094 **(2004)**.
[36] Morten Bogedal, Michael Gleiche, Jean-Charles Guibert, Holger Hoffschulz, Sandrine Locatelli, Ineke Malsch, Mark Morrison, Carole Nicollet, Volker Wagner; Nanotechnology and Its Implications for the Health of the EU Citizen, European Nanotechnology Gateway, **158**, **(2004)**.
[37] B.A.Dani, A.T.Raiche, D.A.Puleo, P.P.DeLuca; AAPS Pharm.Sci.Technol., **3**, E21 **(2002)**.
[38] F.Caruso, R.A.Caruso, H.Mohwald; Chem.Mater., **11**, 3309-3314 **(1999)**.
[39] O.A.Arotiba; Eletrochemical Impedance Modelling of the Reactivities of Dendrimeric Poly(Propylene imine) DNA Nanobiosensors, PhD.Thesis, Dept.of Chemistry, University of the Western Cape, **(2008)**.
[40] Natural-Origin Polymers as Carriers and Scaffolds for Biomolecules and Cell Delivery in Tissue Engineering Applications, Adv.Drug Deliv., **59**, 207-233 **(2007)**.
[41] D.M.Eisenberg, R.B.Davis, S.L.Ettner, S.Appel, S.Wilkey, M.Van Rompay; Trends in Alternative Medicine Use in the United States, 1990-1997 Results of a Follow-Up National Survey, JAMA, **28**, **(1998)**.
[42] M.Sato; Nanophase Hydroxyapatite Coatings for Dental and Orthopedic Applications, PhD.Thesis, Purdue University, **(2006)**.
[43] A.L.Chun, J.G.Moralez, T.J.Webster, H.Fenniri; Biomaterials, **35**, 7304-7309 **(2005)**.
[44] Fujibayashi, S.Neo, M.Kim, H.Kobuko, T.Nakamura; Biomaterials, **254**, 443-450 **(2004)**.
[45] M.Sato, E.B.Slamovich, T.J.Webster; Biomaterials, **26**, 1349-1357 **(2005)**.
[46] R.M.Mardones, R.Talac, A.D.Hanssen, D.G.Lewallen; Use of a Porous Tantalum Revision Shell in Revision Total Hip Arthroplasty, 72nd AAOS Annual Meeting, Washington, **(2005)**.
[47] B.R.Levine, C.J.Della Valle, J.J.Jacobs; J.Am.Acad.Orthop.Surg., **4**, 646-655 **(2006)**.
[48] B.R.Levine, S.Sporer, R.A.Poggie, C.J.Della Valle, J.J.Jacobs; Biomaterials, **27**, 4671-4681 **(2006)**.
[49] H.Matsuno, A.Yokoyama, F.Watari, U.Motohiro, T.Kawasaki; Biomaterials, **22**, 1253-1262 **(2001)**.
[50] C.B.Johansson, H.A.Hansson, T.Albrektsson; Biomaterials, **11**, 277-280 **(1990)**.

[51] P.X.Ma, B.Schloo, D.Mooney, R.Langer; J.Biomed.Mater., **29**, 1587-1595 **(1995)**.
[52] V.Roth, V.C.Mow; J.Bone Joint Surg.Am., **62**, 1102-1117 **(1980)**.
[53] G.Balasundaram, M.Sato, T.J.Webster; Biomaterials, **27**, 2798-2805 **(2006)**.
[54] M.Korbling, Z.Estrov; New England Journal of Medicine, **349**, 570-582 **(2003)**.
[55] Chris Mason, Peter Dunnill; Regenerative Medicine, **3**, 1-5 **(2008)**.
[56] C.A.McDevitt, H.Muir; J.Bone Joint Surg., **58**, 94-101 **(1976)**.
[57] Nickel, J.Dreyer, M.K.Kirsch, T.Sebald; J.Bone Joint Surg., **83**, 7-14 **(2001)**.
[58] S.X.Yuan, L.Fang, Z.L.Chen; Shanghai Journal of Traditional Chinese Medicine, **6**, 38-39 **(2003)**.
[59] M.J.Dalby, S.Childs, M.O.Riehle, H.Johnstone, S.Affrossman, A.S.Curtis; Biomaterials, **24**, 927-935 **(2003)**.
[60] R.L.Price, K.M.Haberstroh, T.J.Webster; Med.Biol.Eng.Comput., **41**, 372-375 **(2003)**.