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Alumina and Zirconia Ceramic for Orthopaedic and Dental Devices

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1. Introduction

Ceramic materials are made of an inorganic non-metallic oxide. Usually ceramics are divided into two groups: silicon ceramics and aluminous ceramics. Ceramics are also divided into crystalline and non-crystalline depending on inner molecular organization. Depending on their *in vivo* behaviour, ceramics are classified as bioresorbable, bioreactive or bioinert. Alumina and zirconia are bioinert ceramics; their low reactivity togheter with their good mechanical features (low wear and high stability) led to use them in many biomedical restorative devices. Their most popular application is in arthroprosthetic joints where they have proven to be very effective, that make their use suitable especially in younger, more active patients. Also dental use of these materials was proposed to achieve aesthetic and reliability of dental restorations.

2. Mechanical and chemical features of bioceramics

2.1 Alumina

Corundum known as α-alumina is the alumina ceramic used for biomedical application,. In nature single crystals of this material are known as ruby if containing Cr2O3 impurities, or as sapphire if containing titanium impurities which give them blue colour. Al_2O_3 molecule is one of the most stable oxides because of high energetic ionic and covalent bonds between Al and O atoms. These strong bonds (Alumina DG(298K) =1580 KJ/mol) leave the ceramic unaffected by galvanic reactions (absence of corrosion, e.g. absence of ion release from bulk materials and from wear debris). Adverse conditions such as strong acidic or alkaline environment at high temperatures didn't corrupt allumina properties. Under compression allumina showed good resistance but under tensile strength shows its brittleness. at room temperature alumina does not show plastic deformation before fracture (e.g. no yield point in stress-strain curve before fracture), and once started fractures progress very rapidly (low toughness K_{IC}).

Tensile strength of alumina improves with higher density and smaller grain size. A careful selection of raw materials and a strict control of production process are performed by manufacturers to optimize allumina mechanical properties. Introduction of low melting MgO in the ceramic process enhanced mass transport during solid state sintering so that

ceramic reached full density at lower temperature. Moreover decreasing grain growth a stronger ceramic was obtained.
Additions of small amounts of Chromia (Cr_2O_3) compensated the reduction of hardness subsequent to the introduction of MgO. CaO content in medical grade alumina devices must be reduced since in wet environment it can compromise its mechanical properties. NaOH impurities in powders obtained by the Bayer process makes allumina unsuitable for the hi-tech biomedical application. Continuous efforts to improve the properties of alumina bioceramics are being made, e.g. by the introduction of high purity raw materials, hot isostatic pressing, proof testing on 100% of manufactured components. The use of hot isostatic pressing (HIP) in bioceramics production minimizes the residual stresses within ceramic pieces and gives ceramics with density close to the theoretical one, improving the strength and reliability of the product. Proof testing of Allumina components consists in the application of internal pressure inducing a stress close to the maximum load bearing capability; when applied to 100% of the parts manufactured, defective products can be eliminated before final inspection. The introduction of laser marking contributed to components traceability due improving the overall quality of the manufacturing process
In 1930 for the first time allumina was used as a biomaterial with the first patent applied by Rock in Germany. Sandhaus in 1965 patented a screw-shaped dental implant made of high alumina powder Degussit AL23. This was the first step in a new era in ceramic engineering. A new dental implant , step-shaped, followed the screw shaped, and was named Tübingen type. But only with the use in orthopaedic purpose in 1970 by Boutin, Allumina was worldwide diffused. He implanted successfully first allumina joints since 1970. Nowadays more than 3 million alumina ball heads have been implanted worldwide. Today, almost 50% of hip arthroplasties performed in Central Europe make use of ceramic ball heads.

2.2 Zirconia

Zirconia, the metal dioxide of zirconium (ZrO_2), was used for a long time as pigment for ceramics; it was identified in 1789 by the German chemist Martin Heinrich Klaproth.
To stabilize zirconium oxide a little amount of non-metallic oxide were added (such as MgO, CaO and Y_2O_3); at a first time magnesia- partially stabilized zirconia (MgPSZ) was the most studied ones, in which a tetragonal phase is present as small acicular precipitates within large cubic grains (Ø40÷50 µm) forming the matrix. But wear properties were badly influenced by this feature; most of the developments were focused on yttria stabilized tetragonal zirconia polycrystal (Y-TZP), a ceramic completely formed by submicron-sized grains, which is today the standard material for clinical applications. Tetragonal grains in Y-TZP ale smaller than 0.5 µm. Tetragonal phase rate retained at room temperature is influenced by: - grains size and on its homogeneous distribution; - the concentration of the yttria stabilizing oxide; - the constraint exerted by the matrix onto grains. The equilibrium among such microstructural parameters influences mechanical features of Y-TZP ceramics. Tetragonal grains can transform in monoclinic, with a 3-4% volume growth of grains: this is the origin of the toughness of the material, e.g. of its ability to dissipate fracture energy. When the pressure on the grains is relieved, i.e. by a crack advancing in the material, the grains near the crack tip shift into monoclinic phase. This gives origin to increased toughness, because the energy of the advancing crack is dissipated at the crack tip in two ways, the first one due to the T-M transformation, the second one due to the need of the crack as it advances to overcome the compression due to the volume expansion of the grains.

In wet environments, over 100°C, tetragonal phase of zirconia ceramics can spontaneously transform into monoclinic. Because this phenomenon starts from the surface of the material, it is possible to report a loss of material density and a reduction in strength and toughness of zirconia. This degradation goes under the name of "ageing" and is due to the progressive spontaneous transformation of the metastable tetragonal phase into the monoclinic phase. Spontaneous T-M transformation in TZP is probably due to the formation of zirconium hydroxides or yttrium hydroxides that promoted phase transition for local stress concentration or variation of the yttrium/zirconium ratio
Swab summarized main steps of TZP ageing in the following way:
The most critical temperature range is 200-300°C.
The effects of ageing are the reduction in strength, toughness and density, and an increase in monoclinic phase content.
Degradation of mechanical properties is due to the T-M transition, taking place with micro and macro-cracking of the material.
T-M transition starts on the surface and progresses into the material bulk.
Reduction in grain size and/or increase in concentration of stabilising oxide reduce the transformation rate.
T-M transformation is enhanced in water or in vapour.
Strength degradation rate is not the same for all TZP ceramics. Swab described that in ten materials tested in presence of water vapour at low temperature, different levels of strength degradation occurred in all the materials but one, where strength remained the same after the treatment. The differences in equilibrium of microstructural parameters like yttria concentration and distribution, grain size, flaw population and distribution in the samples tested caused this variability in ageing behaviour. Strength degradation rate can be controlled by having a high density, small and uniform grain size, a spatial gradient of yttria concentration within grains, introduction of alumina into the matrix. All the above parameters are controlled by the manufacturing process and by the chemical-physic behaviour of the precursors selected for the production of the ceramic. These facts make stability a characteristic of each Y-TZP material and of each manufacturing process.
Hydrothermal treatment has an high risk of phase transition: steam sterilization of zirconia ball heads is not recommended. These process may change the surface finish, reducing wear resistance. Nevertheless, mechanical properties of the material are not altered by these process. Gamma rays or ethylene oxide sterilization are the best choice to manage zirconia biomedical devices. Rare hearth impurities that may be present at part per million (ppm) level within the structure can interact with ionising radiation inducing some changes in colour in ceramic materials. Praseodymium impurities cause a shift to violet of zirconia after irradiation, but the material can return to its ivory colour with heating and putting it under an intense light source; its mechanical properties weren't unaffected by this treatment.
At room temperature Y-TZP ceramic is formed by submicron size grain. during sintering the grains will grow and it is necessary to start from submicron grain size powders and to introduce some sintering aid to limit the phenomenon. The introduction of the stabilizing oxide (yttria Y_2O_3) is a key component in TZP structure at room temperature. hydrothermal stability of the ceramic is enhanced by enriching grain boundaries in yttria: ZrO_2 grains may be yttria coated as in plasma, an alternative to obtain Y-TZP powders by co-precipitation. silica impurities must be avoided because the dissolution of glassy phases at the grain boundaries in wet environment causes the spontaneous transformation of the grains from tetragonal to monoclinic with a loss of mechanical properties. To achieve an

equilibrium a higher toughness and hydrothermal stability must be balanced by a lower bending strength

2.3 Zirconia toughened alumina

Zirconia toughened alumina (ZTA) is obtained adding zirconia up to 25% wt into an alumina matrix. This allow to obtain a class of ceramic materials with increased toughness. These materials, developed in the second half of the seventies are featured by toughness (KIC) up to 12 MPam-1/2 and bending strength up to 700 MPa. Alumina matrix exerts a constraint on the metastable tetragonal zirconia particles maintaining them in the tetragonal state. T-M transformation of the zirconia particles give toughness to this ceramic. Because of different elastic modulus between alumina matrix and the zirconia particles cracks are propagated along zirconia crystals inducing their T-M phase transformation thus dissipating the crack energy. Microcracking of the matrix due to the expansion of the dispersed particles is a further dissipative effect. To ensure the better mechanical performances to this material is mandatory to control the high density of the matrix and the optimisation of the microstructure of the zirconia particles. In this way the maximum amount of metastable phase is retained assuring the transformation of the maximum volume. When hardness is of paramount importance ZTA have some drawbacks: zirconia into the hard alumina matrix results in a decrease in hardness of the ceramic Extensive research has been focussed on ZTA in France and in Italy on ceramics containing up to 80% zirconia, without leading to clinical applications. Allumina can also be toughened by addition of whiskers; but concerns about carcinogenicity of whiskers, and limits in adhesion of the whiskers to the matrix decreased the interest for the biomedical applications of these materials. Elongated grains (platelets), acting as whiskers, can be nucleated within the structure of a ZTA ceramic. This can be obtained by adding e.g. strontium oxide (SrO) to ZTA obtaining SrAl12O19platelets by in situ solid state reaction during sintering. Chromia (Cr2O3), introduced to save the alumina hardness and of Yttria (Y2O3) that acts as stabilizer of the T phase of zirconia in ZTA, leads to a material known as ZPTA(Zirconia Platelet Toughened Alumina) The resulting mechanical properties are very interesting, as wear rates were very low in the laboratory tests, even lower than the ones of alumina and zirconia both on hip and knee simulator studies

ZPTA is a great innovation in ceramic for biomedical devices. Mechanical properties of this new ceramic, allow to develop many innovative ceramic devices.

Property	Unit	Allumina	Y-TZP	ZTA	ZPTA
Density	g/cm^2	3.98	6.08	5.00	4.36
Average grain size	µm	≤1.8	0.3÷0.5	-	-
Bending strength	MPa	>550	1200	900	1150
Compression strenght	MPa	5000	2200	2900	4700
Young modulus	GPa	380	200	285	350
Fracture toughness K_{IC}	$M_{pam}^{-1/2}$	4-5	9	6.9	8.5
Microhardness	HV	2200	1000-1300	1500	1975

Table 1. Selected Properties of load bearing bioceramics for medical devices

3. Biocompatibility

Biocompatibility has been defined as "the ability of a material to perform with an appropriate host response in a specific application". Reaction of bone, soft collagenous tissues and blood are involved in the host response to ceramic implants. Interfacial reaction between these materials and body tissues both *in vitro* and *in vivo* must be considered evaluating biocompatibility of bioinert ceramics. Low rate of tissue reactions towards Alumina are the reason because it is often considered reference in testing orthopaedic ceramic biomaterials. The first experimental data of dense ceramics (ZrO2) *in vivo* biocompatibility in orthopaedic surgery were published 1969 by Helmer and Driskell while the first clinical cases on alumina were described later by Boutin shortly followed by Griss. *In vitro* biocompatibility evaluation of Alumina and Zirconia were performed later than their clinical use. As biocompatibility tests often are reporting the comparison of alumina and zirconia biocompatibility, in the following the results are reviewed in the same manner.

3.1 In vitro tests

Ceramic materials in different physical forms (powders and dense ceramics) were used to perform *in vitro* tests on cell cultures. Absence of acute toxic effects of ceramic in powder and disk form on the different cell lines used in tests both towards allumina both toward zirconia was reported by many studies. *In vitro* assays are influenced by material characteristics, such as the physical form, reactive surface, chemical composition, impurity content etc, as well as by the cell conditions during the tests. Alumina and zirconia disks with 30% of porosity allow adhesion and spreading of 3T3 fibroblasts as observed using SEM. HUVEC and 3T3 fibroblasts osteoblast didn't show any toxic reaction toward Al2O3 or ZrO2 samples (MTT test on cells direct in contact with ceramic particles); the same effects were also observed on ceramic extracts cocultured with fibroblasts. Li, et al demonstrated that powders were more toxic than dense ceramics, using direct contact tests and MTT test with human oral fibroblasts. Ceramic powders can induce apoptosis in macrophages depending on materials concentration as observed by Catelas. Mebouta, et al reported for the first time a different toxic effect between alumina and zirconia: in particular a higher cytotoxicity of alumina particles in comparison to the zirconia ones was measured as human monocytes differentiation; this is probably due to the higher reactive surface of the alumina particles, that were significantly smaller than the zirconia ones

Degidi compared soft tissues reactions to ZrO_2 and titanium; he reported that inflammatory infiltrate, microvessel density and vascular endothelial growth factor expression appeared higher around titanium samples than around ZrO_2 ones. Moreover cellular proliferation on zirconia surface is higher than on titanium ones. Furthermore Warashima reported less proinflammatory mediators(IL-1β, IL-6 and TNF–α) generated by ZrO_2 than titanium or polyethylene.

3.2 In vivo tests

Different physical forms and in different sites of implantation were evaluated in order to analyzing systemic toxicity, adverse reactions of ceramics in soft tissue and/or bone The work of Helmer and Driskell already cited is the first report of implant in bone of zirconia. Pellets were implanted into the monkey's femur, the Authors observed an apparent bone ingrowth without any adverse tissue reaction. Hulbert, et al implantated of porous and non porous disks and tubes in the paraspinal muscles of different ceramics Authors observed ingrowth depending on porous size, and no signs of systemic toxicity. After subcutis, intramuscular or intraperitoneal and intraarticular introduction of alumina and zirconia powders in rats and/or mice mant authors reported the absence of acute systemic adverse tissue reactions to ceramics; similar results were reported after implantation of bars or pins to paraspinal muscles of rabbits or rats and after insertion in bone. bone ceramic interface showed connective tissue presence, progressively transformed in bone direct contact with ceramic. Bortz reported adverse tissue reaction: fibrous tissue in the lumen of zirconia cylinders implanted in dogs and rabbits trachea, and an inflammatory reaction against ceramic powders inserted on PMMA grooves implanted in rabbits femur. In any case this inflammatory reaction was lower than the one observed against CoCr and UHMWPE.

3.3 Carcinogenicity

Griss, et al. in 1973 reported that Alumina and zirconia powders did not induce tumours. They analyzed the long term in vivo reactions to ceramics.

Ames test, and carcinogenicic or mutagenic tests used to study zirconia dishes confirmed that this bioceramic did not elicit any mutagenic effect in vitro. Moreover zirconia radioactivity and its possible carcinogenic effect was also evaluated: radioactivity of the powder is depending on the source of ores used in the production of the chemical precursor of the zirconia powders. Only Ryu RK, et al reported a possible carcinogenic effect of ceramic. They observed association between ceramic and soft tissue sarcoma. Some recent studies have been performed about carcinogenicity of Zirconia Toughened Alumina. Maccauro et al. showed that ZPTA as well as Alumina and Zirconia ceramics did not elicit any in vitro carcinogenic effects; the same group are going to demonstrate the possible carcinogenic in vivo effects of ZPTA.

4. Biomedical applications of zirconia

Several comprehensive reviews on the clinical outcomes of ceramic ball heads for orthopaedical devices are aviable. Jenny, Caton, Oonishi, Hamadouche, demonstrate the favourable behaviour of ceramic biomaterials in reducing the wear of arthroprostheses joints.

THR ball heads
THR acetabular inlays
THR condyles
Finger joints
Spinal spacers
Humeral epiphysis
Hip endoprostheses

Table 2. Orthopaedic medical devices made of bioinert ceramics

Clinical trials demonstrated that ceramic-on-ceramic coupling decreased significantly the amount of wear debris (Boeler,). Nevertheless Wroblesky demonstrated that ceramic in couple with new generation polyethylene may constitute a significant evolution in arthroplasty. This makes ceramics in joints suitable especially in younger patients. The matching of surface roughness, roundness and linearity in the coupling of ceramic tapers with the metallic trunnion plays a relevant role on stresses distribution and intensity, depending also on cone angle, extent of the contact, friction coefficient among the two surfaces Mismatch in female- to-male taper, e.g. due to the many angles in clinical use, roundness, roughness or linearity errors in the taper, are among the most likely "technologic" initiators of ceramic ball head failures. It must be remarked that the mechanical behaviour of ceramic ball heads once installed on the metallic taper depend not only on the ceramic but also on material and design of the taper. Besides the "technologic" failure initiators, several other precautions are necessary when using ceramic ball heads: avoid third body interposition to the ceramic metal, or ceramic/ceramic interface during surgery (e.g.blood clots, bone chips, PMMA cement debris); avoid use of metallic mallets when positioning ball heads on metallic taper (or of alumina inlay into the metal back): use plastic tools provided by the manufacturer or gently push rotate by hand; avoid thermal shocks to ball heads (e.g. dip the ceramic in saline to cool it after autoclave sterilization); avoid application of new ceramic ball heads onto stems damaged during revision surgery. A third important aspect to achieve good arthroprostheses results is surgical technique: both perfect THR component adaptation and orientation, together with soft tissue tension are required. Special care must be taken with orientation, as edge loading of the socket and impingement on components depend on this parameter.

In the past zirconia was highly used in orthopedics; about 900000 zirconia ball heads have been implanted in total hip arthroplasties, even if a debate arose regarding the potential radioactivity and carcinogenicity of zirconia source. But, after the observation of some ball head fractures, zirconia has no longer been used for total hip arthroplasties.

Zirconium oxide is also used as a dental restorative material. Inlays, onlays, single crowns, fixed partial dentures, can be realized using a ZrO_2 core. Moreover, also implant abutment and osteointegrated implant for tooth replacement are available in zirconia.

Realization of dental products requires a preventive project and successive manufacturing in order to satisfy clinical requirement. But, not only individualization is needed: accuracy is absolutely mandatory. Misfits greater than 50 μm are considered unacceptable for dental restorations. Mechanical resistance must be also considered. Frameworks with minimal thickness, often less than 1mm, must be able to sustain chewing stresses. Masticatory load on posterior teeth range from 50N to 250N, while parafunctional behavior such as clenching and bruxism can create loads about 500 and 800N. Zirconia frameworks can bear load between 800 and 3450N. These values are compatible with restorations on posterior teeth if parafunctional loads are not present and a correct framework design is performed .

In order to avoid misfit due to shrinkage during sintering, it is possible to obtain zirconia frameworks by milling full-sintered ZrO_2 samples. This technique is not influenced by sintering problems because zirconia is already sintered, but, anyway, it is influenced by operator accuracy in probe use. CAD/CAM technique is the ultimate opportunity in managing zirconia dental devices production. CAD/CAM is acronym of Computer Aided Design and of Computer Assisted Manufacturing. This system is composed by a digitizing machine to collect information about teeth position and shape, appropriate software for design zirconia restoration and a computer assisted milling machine that cut from a zirconia

sample the desidered framework. This technique reduces human influences allowing obtaining greater accuracy in zirconia core production.
Fully sintered zirconia blocks are very difficult to be grinded. Milling procedures are very slow and requires very effective burs to perform cut in the optimal way. Dimensional stability is granted because there aren't any procedures that can influence volume of framework after milling. On the other hand, grinding reduces significatively toughness of zirconia. This can be due to surfacial stresses during milling. Crystals were induced to transform from tetragonal into monocline reducing T-M phases ratio and consequently toughness. Lutardth measured flexural strength and fracture toughness of zirconia before and after grinding and concluded that mechanical resistance was reduced of about 50% after machining. Also Kosmac studying surface grinding effects on ZrO_2 confirmed these results.
Machining partially sintered zirconia (or green zirconia) presents, on the other hand, different problematics. Green zirconia has a very soft consistency resulting very easy to be milled. Grinding procedures are easy, faster and cheaper. But, after grinding, frameworks must be sintered. This procedure presents some technical problems that require accurate managing to grant a reliable outcome. During Sintering time (about 11 hours) an accurate control of temperature and pressure, especially during cooling phase, is needed to obtain the correct T-M crystals ratio. Moreover, sintering lead to a 20% volumetric shrinkage that must be foresight in advance during designing and milling. For these reasons use of green zirconia results more difficult and expensive: complex designing software and sintering machine are required to obtain accuracy and correct crystal composition. On the other side, if procedures are preformed correctly mechanical resistance results greater than ZrO_2 frameworks milled after sintering]. Moreover sinterization after grinding allows technician also to pigment frameworks helping achieving a satisfying aesthetical outcome.
Ceramic restorations allow an aesthetical outcome more similar to teeth than conventional metal-ceramic ones. Also gingival aesthetic is improved by colour of restoration similar to teeth, that is, together with mucosal thickness the basic parameter for an optimal soft tissue colour outcome. Toughness and colour similar to teeth of zirconia, lead to use this material for different purpose. Zirconiun oxide is used as a reinforce for endocanalar fiber-glass post. Also orthodontic brackets were proposed in ZrO_2. But the most interesting application of this material is nowadays for fixed partial dentures. Single crowns and 3-5 units FPD are described and studied in literature. The continuative search for an optimal metal-free material for prosthetical use found in zirconia an answer for many problems still not solved with other ceramic restorations. Also small dental restorations, like inlays and onlays were proposed with this material. Implanto-prothesical components, such as implant abutment are available with zirconia. Osteointegrated implants for tooth replacement are proposed by some manufacturers, but at the present time there aren't enough studies about behaviour of zirconia implants.
Zirconia restorations have found their indications for FPDs supported by teeth or implants. Single tooth restorations are possible on both anterior and posterior elements because of the mechanical reliability of this material. Mechanical resistance of zirconia FPD was studied on single tooth restorations and on partial dentures. Luthy asserted that Zirconia core could fracture with a 706N load Tinshert reported a fracture loading for ZrO_2 over 2000N, Sundh measured fracture load between 2700-4100N. Zirconia restorations can reach best results as fracture resistance if compared with alumina or lithium disilicate ceramic restorations.

Ageing of Zirconia can have detrimental effects on its mechanical properties. To accelerate this process mechanical stresses and wetness exposure are critical. Ageing on zirconium oxide used for oral rehabilitation is not completely understood. However, an in vitro simulation reported that, although ageing the loss of mechanical features does not influence resistance under clinical acceptable values. Further evaluations are needed because zirconia behavior in long time period is not yet investigated.
On these basis a new family of ceramic material that would complement alumina ceramic where needed. It had to posses the highest possible toughness, the smallest matrix grain size all leading towards improved mechanical reliability but this had to be accomplished without sacrificing the wear resistance and chemical stability of current day alumina ceramics. Alumina Matrix Composites were selected as the best new family of ceramics to provide the foundation for an expanded use of ceramics in orthopaedics. The main characteristics of this Alumina Matrix Composite are its two toughening mechanisms. One is given by in-situ grown platelets which have a hexagonal structure and are homogeneously dispersed in the microstructure. Their task is to deflect any sub-critical cracks created during the lifetime of the ceramic and to give the entire composite stability. The other important characteristic is related to the addition of 17 vol.-% zirconia nano-particles that are dispersed homogeneously and individually in the alumina matrix. This increases strength and toughness of the material to levels equal and in some cases above those seen in pure zirconia. Here, the effect of tetragonal to monoclinic phase transformation is used as a toughening mechanism. In the case of micro-crack initiation the local stress triggers phase transformation at an individual zirconia grain which acts then as an obstacle to further crack propagation. It is a desired behaviour which uses the volume expansion in an attempt to prevent further crack propagation. These two well known effects in material science, crack deflection and transformation toughening give Alumina Matrix Composite a unique strength and toughness unattained by any other ceramic material used in a structural application in the human body.

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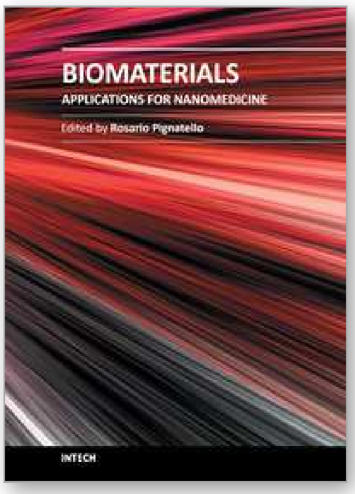

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These contribution books collect reviews and original articles from eminent experts working in the interdisciplinary arena of biomaterial development and use. From their direct and recent experience, the readers can achieve a wide vision on the new and ongoing potentialities of different synthetic and engineered biomaterials. Contributions were selected not based on a direct market or clinical interest, but on results coming from a very fundamental studies. This too will allow to gain a more general view of what and how the various biomaterials can do and work for, along with the methodologies necessary to design, develop and characterize them, without the restrictions necessary imposed by industrial or profit concerns. Biomaterial constructs and supramolecular assemblies have been studied, for example, as drug and protein carriers, tissue scaffolds, or to manage the interactions between artificial devices and the body. In this volume of the biomaterial series have been gathered in particular reviews and papers focusing on the application of new and known macromolecular compounds to nanotechnology and nanomedicine, along with their chemical and mechanical engineering aimed to fit specific biomedical purposes.

How to reference

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