

Multifunctional materials for bone cancer treatment

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Abstract: The purpose of this review is to present the most recent findings in bone tissue engineering. Special attention is given to multifunctional materials based on collagen and collagen–hydroxyapatite composites used for skin and bone cancer treatments. The multifunctionality of these materials was obtained by adding to the base regenerative grafts proper components, such as ferrites (magnetite being the most important representative), cytostatics (cisplatin, carboplatin, vincristine, methotrexate, paclitaxel, doxorubicin), silver nanoparticles, antibiotics (anthracyclines, geldanamycin), and/or analgesics (ibuprofen, fentanyl). The suitability of complex systems for the intended applications was systematically analyzed. The developmental possibilities of multifunctional materials with regenerative and curative roles (antitumoral as well as pain management) in the field of skin and bone cancer treatment are discussed. It is worth mentioning that better materials are likely to be developed by combining conventional and unconventional experimental strategies.

Keywords: bone graft, cancer, collagen, magnetite, cytostatics, silver

Introduction

Bone is one of the naturally occurring composite materials that still does not have an artificial correspondent.¹ The interdependence between its morphology and properties is well understood, and two types of bone structures – cortical (compact) and trabecular (spongy) – can be easily identified. These different morphologies seem to be induced by piezoelectricity, with cortical bone being a result of a mechanically assisted biomineralization process.² The arrangement of osteons along with the loading direction can be explained by piezoelectricity. Recently, Noris-Suárez et al reproduced natural biomineralization conditions in vitro. They proved that the mechanical loading of the collagenous material induces important modifications upon the mineral-deposition process. They demonstrated that once mechanical loading takes place, the collagen fibers became arched and the negative charges appear especially distributed on the compressed zones. This is why mineralization occurs predominantly on the compressed areas, even if no osteoblasts are present.³

Tissue engineering is of interest for researchers especially because of the increasing need for grafting materials.⁴ The starting monolithic materials have been continuously improved by adding different components aimed at inducing new properties or to improve existing ones.^{5–9} The most common improvements have been related to the increase of healing rate, biocompatibility, or mechanical properties, or with the inducing of new properties, such as antimicrobial, anti-inflammatory, or analgesic activity. These new properties are sought after to avoid certain undesirable side effects or infections.^{7,9–11}

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The complex composition and morphology of bone tissues confers them remarkable properties and functionalities.^{1,12–14} In the last few decades, many researchers have invested their efforts in developing new materials for bone grafting inspired in bone composition and structure.¹⁵ The compositions of bone and some of the most studied bone grafts are presented in Table 1. The systematic study of bone grafts can be considered to have started in the early twentieth century, when different transplants were done (allografts and xenografts).¹⁶ Nowadays, special attention is paid to the synthesis of new bone grafts based on composite (nano)materials. Also, many papers deal with the important issue of how to design these materials in order to obtain improved biological properties. Biocompatibility and biointegration are usually realized by using engineered composite (nano)materials starting from natural polymers, calcium phosphates, and bone cells.^{5,6}

Based on the classification made by Ashby et al,¹⁷ nowadays there is a gradual transition occurring from the “nano- and bio-” age to a material-design age. During the nano- and bio-age, scientists focused their attention on improving material properties by decreasing materials’ size to the nanometric scale, but also paid attention to improving biological assessment in order to be better accepted by the human and animal body.¹⁸ The material-design age maintains this principal concern, but improvements are achieved by optimizing such material characteristics as porosity, hydrophilicity, pore size, distribution, and shape, etc.^{19,20} This is why there are a lot of papers dealing with material design or tissue-engineered nanobiomaterials, or even with both concepts.^{5,12,13,21–27} The use of bone cells for

obtaining bone grafts could bring some major advantages: 1) the cells could be gathered from the patient and cultured in vitro; 2) the opportunity for using available stem cells that can be differentiated under proper conditions into bone cells; and 3) bone graft seeded with bone cells has the ability of being easily invaded by new bone ingrowth, thus promoting a much faster integration and the achievement of natural bone properties in a shorter time, in safe conditions, and with less donor tissue compared with classical auto- and allografting procedures.^{36,37} Moreover, the bone graft can act as a drug-delivery system for antibiotics and consequently enhance bone ingrowth in conjunction with wound healing.³⁷

Worldwide, cancer remains the second-most common cause of death, despite the advances in prevention, early detection, and protocols of treatment. It is well known that pain continues to be the most feared complication during treatment.^{38–40} In 2008, the total number of new cancer cases, based on the International Agency for Research on Cancer, was 12,662,554 (52.26% men), while for 2030–21 million new cases of cancer are expected.⁴¹ Mortality is strongly influenced by cancer type. The overall or mortality numbers worldwide in 2008 were 7,564,802 (~59.75% of total incidence). Among the cancer types, the best survival rates (mortality/incidence × 100) are for thyroid and testis cancer (16% and 18%, respectively), while the worst are for liver and pancreas cancer (93% and 96%, respectively).⁴² The very low survival rate is probably strongly influenced by the high mortality induced by lung cancer (which accounts for ~18.2% of total cancer mortalities).⁴³

Cancer usually occurs in mature/old people, except osteosarcoma, which is typically diagnosed in young people (10–20 years old) and rarely in old people,^{44,45} in the extremity of the long bones, especially in the femur.⁴⁶ There are 45 main types of primary bone tumor, the most important being osteosarcoma (35.1% of the primary bone tumors), followed by chondrosarcoma, Ewing’s sarcoma, and chondroma. By sex, males are more exposed to bone cancer (4% incidence in males compared to 3% in females),⁴⁷ even though osteosarcoma develops earlier in females compared with males (by about 2 years).⁴⁶

Cancer treatment is mainly based on surgery and radio- and chemotherapy, but also other unconventional therapies are available: hyperthermia, targeted therapy, immuno- or phototherapy, the use of nanoparticles or stem cell transplants, or many other less used therapies.⁴⁸ Hyperthermia is being used more and more as complementary therapy. The main result of the application of this therapy is decreasing chemotherapeutic doses or levels of radiation needed to

Table 1 Composition of bone and its substitutes

Bone ^{28,29}	50–74 wt% mineral phase; mainly HA 45%–58%, carbonate ~4%, citrate ~0.9%, sodium ~0.7%, magnesium ~0.5%, but also many other trace elements, such as Cl ⁻ , F ⁻ , K ⁺ , Sr ²⁺ , Pb ²⁺ , Zn ²⁺ , Cu ²⁺ , Fe ²⁺ ; 16–40 wt% organic (85%–90% collagen); <10 wt% water
Substitutes ^{29–35}	Metals and alloys (first-generation bone grafts): titanium and its alloys, stainless steel, Co–Cr alloys Ceramics and polymers (second-generation bone grafts): calcium phosphates, Al ₂ O ₃ , ZrO ₂ ; collagen, gelatin, chitosan, chitin, alginate, PLLA, PLGA, PVA, PMMA, PE, PCL (Nano)composite (third-acellular materials and fourth-generation bone grafts, containing cells or derived): COLL/HA, HA/gelatin, HA/chitosan, HA/alginate, HA/PLGA, HA/PLLA, HA/PE, HA/PVA, COLL/PVA/HA

Abbreviations: COLL, collagen; HA, hydroxyapatite; PVA, polyvinyl alcohol; wt, weight; PLGA, polylactide-co-glycolide; PMMA, polymethyl methacrylate; PE, polyethylene; PCL, poly-ε-caprolactone; PLLA, poly-L-lactic acid; Co–Cr alloys, Cobalt–Chrom alloys.

maintain or even improve the efficiency of the treatment.^{49–51} Also, the use of nanoparticles showed a significant antitumoral effect, alone or in association with other therapies.^{52–55} These alternative therapies are mostly in the experimental phase of research, present an exciting challenge for the present, and will probably offer solutions for cancer treatment in the future, but there are also some alternative therapies currently available for cancer treatment, such as Doxil[®] (Janssen, Beerse, Belgium) and Abraxane[®] (Celgene, Summit, NJ, USA).⁵⁵

Drug-delivery systems are also used for different kinds of cancer. The most popular drug-delivery systems are based on polymers and ceramics and their composites. Polymers are by far the most used drug-delivery systems, the most used being polyethylene glycol (PEG), polyethylene oxide, poly-ε-caprolactone, chitosan, alginate, polyvinyl alcohol (PVA), polymethyl methacrylate, cellulose, etc.^{56–67} Also, proteins (collagen being the most abundant) are known as support for drug-delivery systems, but usually their high chemical and physical instability present technical problems related to synthesis and storage.^{68–71} PVA is extremely useful for chemoembolization, and in certain conditions can be loaded with various antitumoral drugs, such as cisplatin, doxorubicin, mitomycin C, and ethiodol.^{67,72–74} Ceramic drug-delivery systems are also used for the treatment of bone cancer.⁷⁵

Collagen–hydroxyapatite composite materials

Collagen is a special class of proteins present in many tissues and organs. The history of collagen starts in 1960 with the discovery of the first representative of this class. Currently, 29 types of collagen⁷⁶ are known. From the point of view of distribution and biomedical applications, type I collagen is by far the most abundant and used variety. The intensive use of type I collagen can be easily explained based on the following: 1) there are a large number of type I collagen precursors (especially bovine calf); 2) the extraction technology is convenient (even native, fibrillar collagen is obtained under controlled conditions, collagen being susceptible to denaturation), because of the short extraction time with cheap reactants, especially if compared with the technology of extraction of type V collagen from bone.^{77–79} In the case of bone, a supplementary step is required, which consists of bone decalcification with hydrochloric acid and/or ethylenediaminetetraacetic acid.^{80–82} Once extracted, the native or denatured collagen can be stored as gel or transformed in fibers or matrices.⁷⁷

It is worth mentioning that type I collagen is also commercially available and used as wound dressing, especially in

the case of burns,^{83,84} as a main component of many creams designed for care or treatment of skin laxity, rhytides, or photoaging,⁸⁵ or as a component of many engineered materials used for bone regeneration and cancer treatment.^{70,78,86,87} Collagen has also been used since 1980 as a drug-delivery system for ophthalmic agents (especially the antibiotics gentamicin and vancomycin),⁸⁸ the trend being to extend the use of this material in obtaining many other drug-delivery systems.^{71,78,89}

Despite intensive research efforts in the field of bone and bone grafts,^{29,90–94} the properties of the materials obtained are still far from those of healthy bone.⁹⁵ Many types of materials have been separately attempted as bone grafts, such as ceramics^{32,96,97} and polymers,^{98,99} or combined in different manners to obtain composite materials.^{12,22,23,27,29,93,100–108} Collagen–hydroxyapatite (COLL/HA) composites are desired materials for bone grafting, especially due to their very good compositional similarity with bone,^{1,28} but also as drug-delivery systems.^{109–113} COLL/HA composite materials are currently extensively used as bone grafts.^{12,21,33,34,93,100–108,114–117} Obviously, the biological properties as well as the mechanical properties are influenced by the manufacturing process. The size and crystallinity of hydroxyapatite crystals are essential parameters that influence the biological properties,^{95,118} materials based on smaller crystals inducing less inflammatory response.⁹⁵

Most studied are the porous COLL/HA composite materials, which could be considered especially for trabecular bone grafting and reconstruction, but can also be used for compact bone reconstruction. The biointegration of COLL/HA scaffolds is strongly influenced by porosity and pore size. Generally, it can be assumed that 150–200 μm pores are optimal for rapid osteointegration.¹¹⁹ Larger pores are unwanted, because the mechanical properties of the graft drastically decrease, while narrower pores limit cell penetration inside the graft.^{120,121} Porosity and pore size can be controlled by different parameters, such as precursor concentration, drying conditions, presence of different components, etc.^{13,22} Usually, COLL/HA composite materials with high porosity are obtained from diluted, mineralized collagen gel followed by freeze-drying. Control of porosity can easily be achieved by controlling the drying process, (eg, air-drying followed by freeze-drying).¹³ It has been proved that porosity decreases upon increase in air-drying time/extent.^{12,13} The explanation is very simple: air-drying is driven by capillary action that makes the material shrink and become denser during the evaporation of liquid water.¹² Conversely, capillary forces are absent in freeze-drying, which involves sublimation of

frozen water, therefore maintaining the initial morphology of the porous structure. Based on literature data published by us,¹³ the evolution of the porosity of samples obtained by combined drying is presented in Table 2, and ranges between 95% and 38%.

More compact composite materials are usually obtained from collagen gel by mineralization under such conditions that allow continuous material restructuring (Table 2, sample SA, COLL-PVA 1:2 A, or COLL-PVA/HA 1:2:3 A). Porosity can fall below even 5% if centrifugal sedimentation is used and only then dried in air.

Figure 1 presents the morphology of some COLL/HA composite materials obtained by mineralization of collagen in different forms (gel, matrix, or fiber).^{12,21,115} From collagen gel, both porous and compact materials as well as materials with intermediate porosity can be obtained. The mineralization of collagen matrix usually leads to porous composite materials. Probably, under certain conditions, collagen matrices and fibers can be processed to more compact materials. Porous composite materials have been tested as drug-delivery systems because, similarly with natural bone, the exchange rate (here the release rate) of the porous materials is higher than the release rate from compact materials.

Multifunctional materials

A lot of materials have been tested as delivery support for bone-related diseases. A short review on this specific topic was recently published by Soundrapandian et al.¹²²

Table 2 Influence of preparation route and composition on the porosity of different samples

Sample	Porosity, %	Observations
CAD 0	95	CAD samples obtained
CAD 30	94	by controlled air-drying,
CAD 48	93	followed by freeze-drying
CAD 76	92	Data extracted from
CAD 96	88	Andronesco et al ¹³
CAD 173	54	
CAD 199	38	
SA	16	COLL/HA material obtained by self-assembly ¹² (data not presented in that manuscript)
COLL-PVA 1:2 L	93	"L" samples obtained by
COLL-PVA 1:2 A	19	freeze-drying
COLL-PVA/HA 1:2:3 L	79	"A" samples obtained by
COLL-PVA/HA 1:2:3 A	14	air-drying
COLL/HA centrifugation	3	Data extracted from Ficai et al ⁵ COLL/HA material obtained by mineralization followed by centrifugal sedimentation (data not published)

Abbreviations: COLL, collagen; HA, hydroxyapatite; PVA, polyvinyl alcohol.

Most of these drug-delivery systems are based on the combination of different polymers with bioglass or calcium phosphates. Even if natural polymers are more suitable, a lot of composite materials based on synthetic polymers, such as polycaprolactone, poly(D,L-lactide), polylactide-co-glycolide (PLGA), or polymethyl methacrylate, have been also regarded with increasing interest.^{122–124} The enhanced stability of synthetic polymers in comparison with natural ones explains the higher number of composite materials based on synthetic polymer matrices. Further, the possibility of tailoring the composition of synthetic polymers enables a broader range of properties to be obtained for the final composites, including mechanical properties, drug-release rate, etc.

Starting from the well-established materials for bone grafting, different kinds of natural or synthetic components (Table 3) have been added in order to induce some new functionalities. Multifunctional materials are being regarded with increasing interest for both industrial and biomedical applications.^{125,126} The multifunctional features of collagen and COLL/HA composite materials can be induced by the incorporation of various components, such as bone morphogenic protein,^{127–131} vitamins,^{110,132} bisphosphonates,^{111,133} antibiotics,^{69,112,113} magnetite,¹¹⁶ cytostatics,⁷⁰ or even more complex systems.¹³⁴ A main functionality of many of these systems is related to their ability to deliver the active component. Perhaps the most studied drug-delivery systems are those loaded with antibiotics or analgesics.¹³⁴ For the treatment of severe bone defects, surgical intervention might be required, because otherwise self-healing would be very slow, or even abnormal repair could happen.²⁹ The current protocols in the case of surgical intervention include the administration of antibiotics. A better alternate is to use bone grafts with antibacterial activity (for instance, an antibiotic-loaded bone graft), because the local delivery of the antibiotic reduces the systemic toxicity of these drugs.^{135,136} The use of analgesic-loaded materials is a real need in the treatment of many diseases. In some cases, drug-loaded systems are easy to apply clinically. For instance, in the case of bone cancer, resection of the tumoral tissue is often required, leaving a bone defect that needs to be filled with bone-regenerative material. Bone fillers can in fact be more complex systems incorporating pharmaceutically active substances (analgesic and/or antitumoral drugs), allowing them to be released in situ.^{70,134} Generally, the presented multifunctional systems were developed in order to assist natural repair mechanisms (bone morphogenic protein presence improves the rate of bone regeneration, bisphosphonate indirectly favors bone formation by suppressing bone resorption) or even to act as

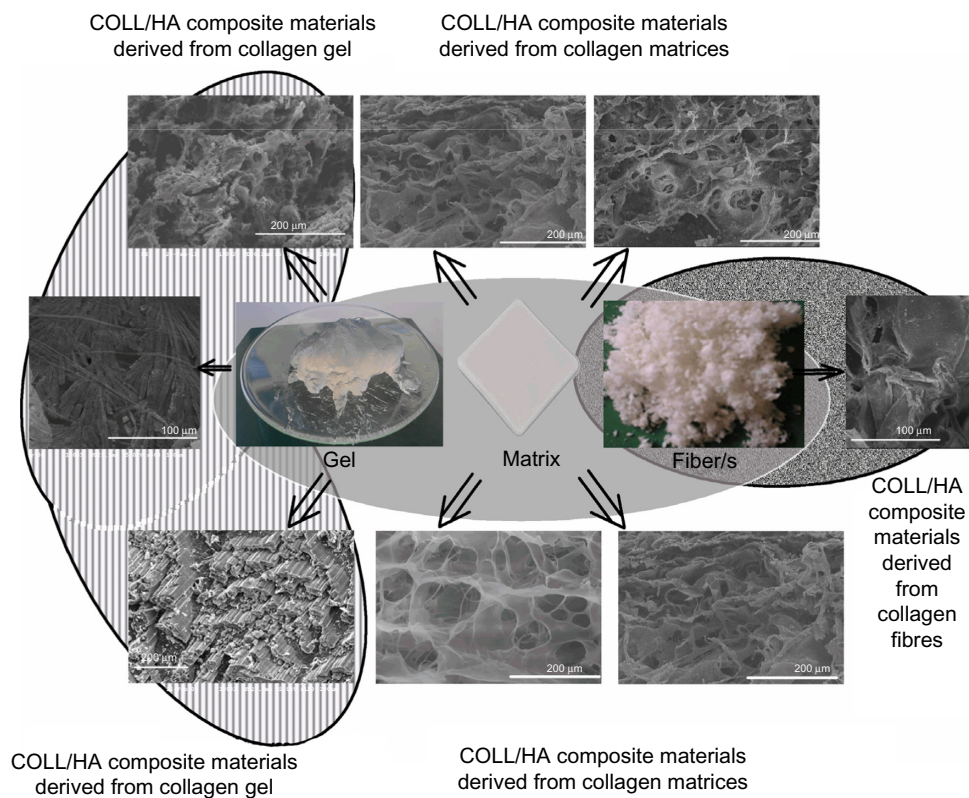


Figure 1 Collagen (COLL) forms and their COLL/hydroxyapatite (HA) composite (nano)materials.

Notes: Reprinted from *Chem Eng J*.160. Fikai A, Andronescu E, Voicu G, et al. Self assembled collagen/ hydroxyapatite composite materials. 794–800. Copyright (2010), with permission from Elsevier.¹² Reprinted from *Mater Lett*. 64. Fikai A, Andronescu E, Trandafir V, Ghitulica C, Voicu G. Collagen/hydroxyapatite composite obtained by electric field orientation. 541–544. Copyright (2010), with permission from Elsevier.²¹ Adapted from Golub LM. Special Issue: Clinical Applications of Non-Antibacterial Tetracyclines Introduction. *Pharmacol Res*. 2011;63:99–101.¹¹⁴

drugs (for avoiding infections [antibiotics] or even to fight against cancer [cytostatics] or other bone-related diseases). All these systems can be assimilated with drug-delivery systems and could be used to treat diseases from simple bone defects/fractures up to bone cancer. It is expected that clinical trials will be positive, because local administration will improve drug efficiency and limit side effects.^{70,137}

Drug-delivery systems for bone cancer treatment

Research on cancer treatment has focused on two main areas: 1) developing new drugs, and 2) improving the activity of existing drugs by reducing their side effects. The main strategy for improving the activity of antitumoral agents is local delivery. A lot of drug-delivery systems were proposed and tested between 1991 and 2013,¹³⁸ such as PLGA/doxorubicin,¹³⁹ chitosan/paclitaxel,¹⁴⁰ polyurethane/curcumin,¹⁴¹ chitosan/ellagic acid,¹⁴² alginate/cisplatin,⁶² poly-L-lactic acid/paclitaxel,¹⁴³ PLGA/isopropyl myristate/paclitaxel,¹⁴³ PEG–poly(aspartic acid)/adriamycin,¹⁴⁴ gelatin/doxorubicin,¹⁴⁵ hydroxyapatite/platinum complexes,^{146,147} or COLL/HA/cisplatin.⁷⁰

Apatite-based materials are extensively used as bone filler/grafts.^{148–150} This is why many drug-delivery systems designed for bone-disease treatment are based on hydroxyapatite. For instance, hydroxyapatite/cisplatin drug-delivery systems were obtained and tested as delivery systems of different platinum complexes.^{147,151–154} Many trials were taken into account, focusing on the synthesis route, drug content, porosity, pore size, etc. Hydroxyapatite samples with different porosity fractions (58%, 76%, and 82%) and average pore sizes (15 μm, 21 μm, and 35 μm) were obtained by the gel-casting method followed by cisplatin loading.¹⁴⁷ Percentage cisplatin recovery after 168 hours increased from 21% to 28% and 42% as porosity fractions increased within the aforementioned range (58%–82%). Control of the release rate is of paramount importance, because long-term delivery could decrease cancer recurrence by reducing remnant cancerous cells.⁷⁰

Recently, Abe et al developed new paclitaxel-loaded hydroxyapatite/alginate composite material for the treatment of metastatic spine cancer,¹⁵³ which develops frequently in patients with breast cancer. Based on animal experiments, the use of paclitaxel-loaded hydroxyapatite/alginate composite

Table 3 Common components used for inducing bone graft multifunctionality

Component	Observations	References
Collagen	Support material for tissue regeneration (especially skin-tissue regeneration)	83,84
Hydroxyapatite	Support material for tissue regeneration (especially for bone-tissue regeneration)	95
BMPs	Improve bone regeneration	127–131 155–158
Bisphosphonate	Synthetic compounds that are taken up preferentially by the skeleton and suppress osteoclast-mediated bone resorption	133,159
Vitamins	1,25 Dihydroxycholecalciferol (D3) – calcium homeostasis Vitamin K – responsible with bone mineralization	160 109,132, 160
Antibiotics	Antibacterial purpose (gentamicin, norfloxacin, ciprofloxacin, vancomycin)	111,112, 161
Analgesics	Local analgesics are used especially for pain management	14
Nanoparticles		
Magnetite	Cancer therapy by hyperthermia Magnetic resonance imaging Drug delivery and targeted delivery	116,162,163 164,165 165–167
Silver	Antibacterial and antitumoral effects	168–172
Cytostatics	Antitumoral effects	70,173–175
Glycosaminoglycans (hyaluronan and chondroitin sulphate)	– modulate the attraction of skin and bone precursor cells and their subsequent differentiation and gene expression – regulate the action of proteins essential to bone and skin regeneration	176,177

beads led to 140%–150% increases in disease-free time as well as survival time compared with control animals.

Itokazu et al developed some drug-delivery systems based on hydroxyapatite and cytostatics for bone cancer treatment.^{177–179} They proved that porosity and pore size influenced the release rate of both doxorubicin and methotrexate. The implantation of these ceramic blocks at the tumor site led to a reduction in dose of the antitumor agent, and consequently the risk of systemic toxicity decreased drastically compared with conventional systemic administration. The improved contact of antitumor agents with tumoral cells is expected to reduce the recurrence and metastasis of cancer.

A gelatin/doxorubicin drug-delivery system¹⁴⁵ was obtained and tested for the treatment of bone cancer,

because doxorubicin is one of the most potent antitumor agents in use for bone cancer treatment, while the gelatin could act, after doxorubicin release, as a scaffold for bone regeneration. The classical administration route of doxorubicin is undesirable because of severe side effects. A general way to reduce side effects is to avoid intravenous administration of antitumor agents by using drug-delivery systems. In the case of bone cancer, the use of implantable gelatin/doxorubicin could be a promising way of targeted delivery of doxorubicin to tumoral tissue. The rate of delivery could be easily controlled by the degree of cross-linking and porosity.

COLL/HA–cisplatin is a remarkable material for the treatment of bone cancer because it assures two functions: targeted delivery of cisplatin and acting as a regenerative scaffold.⁷⁰ For this reason, samples were obtained and tested from the point of view of cisplatin-induced cytotoxicity. The delivery curve of cisplatin has two independent regions: a fast delivery up to 2 hours, followed by a sustained delivery of cisplatin up to 26 hours.⁷⁰ The short release time can be exploited by choosing a proper polychemotherapeutic method that includes the cisplatin release and further traditional administration of complementary cytostatics.¹⁸¹

Bone cancer is usually associated with terrible pain.^{182–184} Up to 30% of patients with recently diagnosed cancers report pain. With the evolution of the cancer, the pain becomes more intense, and about 80% of patients with primary bone cancer and over 90% of patients with metastases to osseous structures need ever-stronger drugs for pain management.^{39,185–187} Based on the World Health Organization analysis, pain intensity as well as pain management is classified at three levels. The lowest level of pain is usually treated with nonopioid and/or adjuvant drugs (aspirin and acetaminophen being extensively used), the middle and worst levels of pain need increasing doses of opioids (and also with increasing efficiency from weak [codeine, for instance] to strong opioids [morphine, for instance]) combined or not with nonopioid and/or adjuvant drugs.¹⁸⁶ In the case of severe pain, systems with immediate or sustained release are used.¹⁸⁷

Magnetite and magnetite-based materials for bone cancer treatment

An overview of the most important applications of magnetite and magnetite-based materials is presented in Figure 2. Pure magnetite is rarely used for cancer treatment, in particular because of its high tendency of agglomeration and high reactivity. This is why many researchers have attempted to functionalize its surface from simple fatty acids,¹⁸⁸ up to

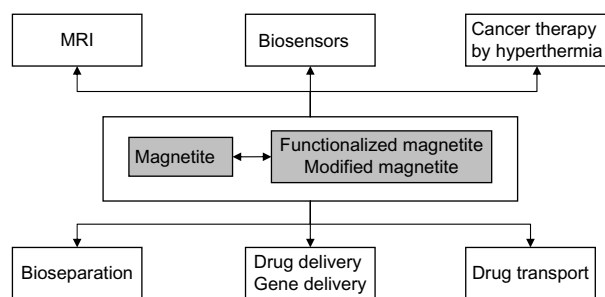


Figure 2 Applications of magnetite and magnetite-based materials.
Abbreviation: MRI, magnetic resonance imaging.

complex agents, such as aminophosphonic acid, diols and polyols, polyhydroxy acids, siloxanes, thioacids, etc.¹⁸⁹ As presented in Figure 2, magnetite and magnetite-based materials are efficient in cancer diagnosis as well as in cancer treatment, including hyperthermia as well as drug transport and targeted delivery. The hyperthermia is produced by magnetite when a proper alternating electromagnetic field is applied. The output power and the applied frequency are essential for producing medical hyperthermia, especially in the case of deep organs/tissues.¹⁹⁰ Usually, these radiations are of low power and should induce low toxicity.¹⁹¹

Magnetic materials proved its effectiveness in the treatment of different diseases, including cancer treatment, by combining surgery – as a conventional treatment and hyperthermia – as an alternate route of treatment. A methodology of treating bone cancer was presented by Andronescu et al,¹¹⁶ (Figure 3) and consists of two main parts. The first step is assimilated with the surgical intervention of resection of the tumoral tissue, while the second step consists of filling the resulting bone defect with multifunctional materials. Once implanted, bone healing starts due to the presence of COLL/HA composite material. The magnetic nanoparticles can be activated, externally and at any time, by applying an electromagnetic field that induces hyperthermia.

Even if only a few materials are based on COLL/HA-Fe₃O₄,^{116,134} perhaps, due to the high sensibility of the

collagenous structure, their potential is great. The work realized by Andronescu et al¹¹⁶ presents the preparation of different COLL/HA-Fe₃O₄ with a 1:4 ratio of COLL:HA and 1%, 2%, and 5% magnetite. The in vitro studies revealed that mild hyperthermia is produced even at low magnetite content. In the case of COLL/HA-Fe₃O₄ with 1% magnetite, the maximum temperature reached was ~41°C, which means mild hyperthermia, while at 5% magnetite the maximum temperature exceeded 45°C (Figure 4). All these data were obtained using thermostated samples (37°C) at 150 kHz.

The aforementioned methodology of bone cancer treatment can be easily adapted for more complex material drug-delivery systems, such as COLL/HA-Fe₃O₄-cytostatic, COLL/HA-Fe₃O₄-analgesic, COLL/HA-Fe₃O₄-Me (Me = Au, Ag), COLL/HA-Fe₃O₄-Me-cytostatic, COLL/HA-Fe₃O₄-Me-analgesic, or even COLL/HA-Fe₃O₄-Me-analgesic-cytostatic.¹³⁴ These multifunctional materials assure the convergence of conventional (surgery and chemotherapy) and alternative (hyperthermia, antitumoral effect of some metallic nanoparticles, phototherapy, and pain management due to the presence of analgesics) routes of bone cancer treatment. It is expected that due to the unconventional component of bone cancer treatment (as well as the targeted delivery of chemotherapeutic drugs) that the content of chemotherapeutic drugs will decrease and consequently systemic toxicity will be minimized.

For instance, Campbell et al¹⁹² synthesized quasicubic magnetite/silica core-shell nanoparticles that proved to be enhanced magnetic resonance imaging (MRI) contrast agents for cancer imaging. The synthesis of Fe₃O₄@SiO₂ was performed from prefabricated magnetite nanoparticles by controlled hydrolysis of Tetraethylorthosilicate with the formation of a silica network onto the magnetite nanoparticles. Using these quasicubic magnetite/silica nanoparticles, in vitro and in vivo experiments were carried out. Based on the in vivo experiments on mice infected with PC3 human prostate cancer cells, the change in MRI signal was up to

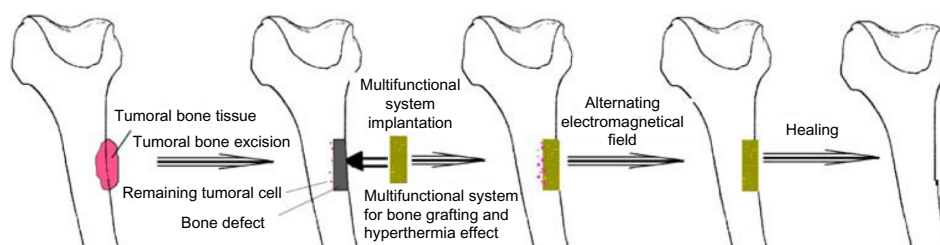


Figure 3 Schematic representation of bone cancer treatment by combined therapy (surgery and hyperthermia).

Note: With kind permission from Springer Science+Business Media: *J Mater Sci—Mater M.*, Synthesis and characterization of collagen/hydroxyapatite:magnetite composite material for bone cancer treatment. 21, 2010, 2237–2242, Andronescu E, Fikai M, Voicu G, Fikai D, Maganu M, Fikai A, figure 2.¹¹⁶

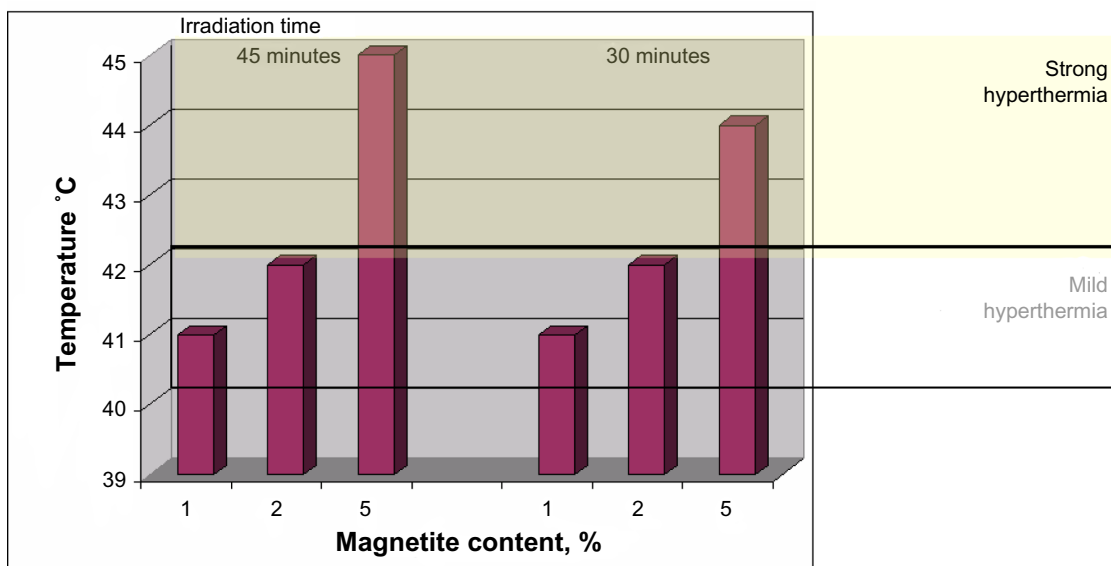


Figure 4 Hyperthermia versus content of magnetite.

Note: Data from Andronescu E et al.¹¹⁶

80% for 100 $\mu\text{g/mL}$ Fe, a value that is significantly higher than reported results obtained with other materials, which reach up to only 15%–20%. The presence of silica led to a higher uptake of PC3 prostate cancer cells compared with pure magnetite. PC3 prostate cancer cell viability decreased once the content of Fe increased from 0 to 100 $\mu\text{g/mL}$.¹⁹¹

Treating bone cancer with magnetite and/or magnetite-based materials has also been attempted with different materials, such as polymethyl methacrylate/ Fe_3O_4 ,^{193,194} HA/ Fe_3O_4 ,^{195–198} glass- and bioglass-based composites,^{199,200} and complex polymer/ceramic composite materials with various magnetite content.^{116,201,202} Based on the literature survey, most materials designed for bone cancer treatment by hyperthermia are based on calcium phosphates or bioglass and magnetite.

Conclusion and perspectives

Cancer remains the second-most common cause of death in the world, despite advances in prevention and early detection and newer treatment protocols. The development of new antitumoral agents as well as the development of more efficient treatment strategies are current pursuits for scientists. Chitosan and PEG have been intensively studied for drug delivery in many applications, including cancer treatment. Only a few papers have dealt with collagen-based support materials, most probably because of the high chemical sensibility of this protein in comparison with chitosan, PEG, alginate, etc. It is expected that the use of collagen for

the preparation of drug-delivery systems of cytostatics will be continued in the future. Expected applications are bone cancer treatment by using composite materials based on collagen and calcium phosphates, skin cancer treatment by using collagen-based polymeric materials, or even colon cancer, collagen being a good carrier through the stomach.

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Disclosure

The authors report no conflicts of interest in this work.

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