A microparticle includes a plurality of magnetic nanoparticles having a Curie temperature between 40° and 100° C. The microparticle further includes a biocompatible polymer and/or biocompatible ceramic and a plurality of radiopaque nanoparticles.
DEVICES AND METHODS FOR THERAPEUTIC HEAT TREATMENT

CROSS-REFERENCE TO RELATED APPLICATIONS

The following commonly assigned patent applications are incorporated herein by reference, each in its entirety:


U.S. Pat. App. Ser. No. 61/980,952 (Sutermeister et al), entitled MEDICAL DEVICES FOR THERAPEUTIC HEAT TREATMENTS, filed on April 17, 2014; and

U.S. Pat. App. Ser. No. 61/981,003 (Sutermeister et al), entitled COMPOSITIONS FOR THERAPEUTIC HEAT DELIVERY, filed on April 17, 2014 and

U.S. Pat. App. Ser. No. 61/980,936 (Sutermeister et al), entitled DEVICES AND METHODS FOR THERAPEUTIC HEAT TREATMENT, filed on April 17, 2014.

TECHNICAL FIELD

The present disclosure pertains to medical devices, systems, and methods for therapeutic treatment using heat. More particularly, the present disclosure pertains to heat treatment of tumors and other undesirable tissues.

BACKGROUND

Body tissues may undesirably grow or swell due to unregulated cell division, resulting in the formation of benign, pre-malignant, or malignant tumors. Such tumors are generally treated by a variety of therapeutic approaches such as excision, chemotherapy, radiotherapy, or a combination of these approaches. Each approach has limitations affecting its clinical utility. For example, excision may not be appropriate where the tumor presents as a diffuse mass or is in a surgically inoperable location. Chemotherapeutic agents are generally non-specific, thus resulting in the death of both normal and diseased cells. Radiotherapy is also non-specific and results in the death of normal tissues exposed to ionizing radiation. In addition, the core of a
tumor mass may be relatively resistant to ionizing radiation or chemotherapeutic agents.

Typically, hyperthermia is used for treating tumors alongside the above therapeutic approaches or as a standalone therapy. Known hyperthermia treatments suffer from a number of potential risks. For example, in addition to heating cancer cells, known hyperthermia treatments tend to heat the surrounding healthy cells. Depending upon the hyperthermia treatment, the damage to healthy cells can be at least somewhat widespread.

Consequently, there remains a need for devices and methods for effective heat treatment of tumors and undesirable tissues with robust and precise temperature control with localized focus.

**SUMMARY**

In some embodiments a catheter includes a catheter shaft, a handle portion, and a plurality of microparticles. The catheter shaft defines a lumen and has a distal end portion, which includes an elastic orifice. The elastic orifice has a closed configuration and an open configuration. The handle portion defines a reservoir that is in communication with the lumen and stores a liquid composition. In some embodiments, the liquid composition is a saline solution. The microparticles include a metallic component having a Curie temperature between 35° and 100° C. The microparticles are configured to travel through the lumen and have a cross-section larger than the cross-section of the elastic orifice when the elastic orifice is in the closed configuration.

In some embodiments, an implantable therapeutic device has a metallic portion, a first thermoplastic polymer portion, and a therapeutic drug. The metallic portion has a Curie temperature. The first thermoplastic polymer portion at least partially encases the therapeutic drug and has a melting temperature less than the Curie temperature of the metallic portion, wherein heating of the metallic portion to the Curie temperature melts the first thermoplastic polymer portion and releases the drug.

In some embodiments a microparticle includes an inner portion and an outer portion surrounding the inner portion. The inner portion includes a biocompatible polymer and/or biocompatible ceramic and a plurality of magnetic nanoparticles having a Curie temperature between 40° and 100° C. The outer portion includes a
biocompatible polymer and/or biocompatible ceramic and a plurality of radiopaque nanoparticles.

In some embodiments, a method of treating a medical condition inside a body cavity or lumen includes inserting a first plurality of microseeds into the body cavity or lumen. The microseeds of the first plurality of microseeds have a diameter of 1-30 microns and a Curie temperature between 30° and 440° C. The method further includes inserting a second plurality of microseeds into the body cavity or lumen subsequent to the first plurality of microseeds. The microseeds of the second plurality of microseeds have a diameter of 30 microns to 1000 microns and a Curie temperature between 30° and 440° C. The first plurality of microseeds is configured to perform a different function within the body cavity or lumen than the second plurality of microseeds.

The above summary of some embodiments is not intended to describe each disclosed embodiment or every implementation of the present disclosure. The Figures, and Detailed Description, which follow, more particularly exemplify these embodiments.

**BRIEF DESCRIPTION OF THE DRAWINGS**

A detailed description of the invention is hereafter described with specific reference being made to the drawings.

FIG. 1 is a cross-sectional view of an embodiment of a microparticle;

FIGs. 2A and 2B are cross-sectional views of an embodiment of an implantable therapeutic device in a closed configuration and an open configuration, respectively;

FIGs. 3A and 3B are cross-sectional views of an embodiment of an implantable therapeutic device in a closed configuration and an open configuration, respectively;

FIG. 4 illustrates an embodiment of an implantable therapeutic device;

FIG. 5 illustrates an embodiment of an implantable therapeutic device;

FIGs. 6-8 are schematic illustrations of catheters for delivering implantable therapeutic devices;

FIG. 9 shows a schematic illustration of the catheter of FIG. 6 within a body lumen;
FIG. 10 shows a schematic illustration of the catheter of FIG. 7 within a body lumen;
FIG. 11 shows a detailed schematic view of a portion of the catheter of FIG. 6;
FIG. 12 shows a detailed schematic view of a tissue site;
FIGs. 13A and 13B illustrate radiofrequency (RF) pulses, as applied over time, to the implantable therapeutic devices;
FIG. 14 illustrates implantable therapeutic devices in body tissue; and
FIG. 15 illustrates a distributed antenna array for delivering signals to the implantable therapeutic devices of FIG. 14.

While the disclosure is amenable to various modifications and alternative forms, specifics have been shown by way of example in the drawings and will be described in detail. It should be understood, however, that the intention is not to limit the invention to the particular embodiments described. On the contrary, the intention is to cover all modifications, equivalents, and alternatives falling within the spirit and scope of the disclosure.

DETAILED DESCRIPTION

Hyperthermia provides localized thermal treatment of tumor cells and lacks any cumulative toxicity in contrast to chemotherapy and radiotherapy. A variety of hyperthermia therapeutic approaches are used for treatment of tumors. One such approach involves deployment of magnetic nanoparticles to a tumor site. These magnetic nanoparticles have a selected Curie temperature and generate heat when subjected to an applied alternating field. While the present disclosure is discussed relative to the thermal treatment of tumor cells, it is contemplated that the devices and methods described herein can be applied to other parts of the anatomy where hyperthermia treatments or the controlled application of heat is desired. For example, the devices and methods may be applied to other parts of the anatomy, such as, but not limited to, the vasculature, the nervous system, gastrointestinal, urological, gynecological, etc.

Although the magnetic nanoparticles provide non-invasive localized heating of the tumor, random and unknown distribution of magnetic nanoparticles over the volume of the tumor disrupts homogeneous heating of the tumor for treatment. Moreover, heating of such magnetic nanoparticles usually raises their temperature over a small, fixed range, as defined by the Curie temperature of the magnetic
nanoparticles. Such limited and fixed temperature range may not be sufficient to
induce the requisite therapeutic effect for treatment.

The recitation or disclosure of numerical ranges by endpoints includes all
numbers within that range (e.g., 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.80, 4, and 5).

As used in this specification and the appended claims, the singular forms "a",
"an", and "the" include plural referents unless the content clearly dictates otherwise.
As used in this specification and the appended claims, the term "or" is generally
employed in its sense including "and/or" unless the content clearly dictates otherwise.

References in the specification to "an embodiment", "some embodiments",
"other embodiments", etc., indicate that an embodiment includes a particular feature,
structure, or characteristic, but every embodiment may not necessarily include the
particular feature, structure, or characteristic. Moreover, such phrases do not
necessarily refer to the same embodiment. Further, when a particular feature,
structure, or characteristic is described in connection with an embodiment, it should
be understood that such feature, structure, or characteristic may also be used in
connection with other embodiments, whether or not explicitly described unless clearly
evidenced or stated to the contrary.

"Curie temperature" is defined as the temperature at which permanent
magnetic properties of a material convert into induced magnetic properties, or vice
versa.

"Curie materials" refer to those metals or metal alloys that exhibit magnetic
properties based on selected Curie temperatures. The Curie temperature of a Curie
material may be altered by using composite materials, which may or may not be
ferromagnetic. Changes in doping, additives, composites, alloying, and density of
Curie materials can alter the structure and behavior of the Curie material and the
Curie temperature.

As used herein, a "thermoset" polymer (e.g., a thermoset) refers to a polymer
that, once having been cured (or hardened) by a chemical reaction (e.g., covalent bond
forming, crosslinking, etc.), will not soften or melt when subsequently heated.

As used herein, a "thermoplastic" polymer (e.g., a thermoplast) refers to a
polymeric material that softens when heated and hardens upon cooling, processes that
are reversible and repeatable.

As used herein, "particle size" of a particle refers to the largest dimension
(chosen from length, width, and height) of the particle. For example, for a spherical
particle, the largest dimension is the diameter. As used herein, the "particle size" of a plurality of particles refers to the average (i.e., mean) of the particle sizes of the particles, based on the population of particles. As used herein, a "range of particle size" of a plurality of particles refers to a range in which at least ninety percent of the population of particles has a particle size within that range, allowing for a combined up to ten percent of the population of particles to be above the recited range and below the recited range. For example, a range of particle size of a plurality of particles of from 1 nanometer to 100 nanometers refers to a plurality of particles wherein at least ninety percent of the population of particles has a particle size from 1 nanometer to 100 nanometers (meaning that the sum of the populations of particles less than 1 nanometer and particles greater than 100 nanometers does not exceed 10% of the total population), with 0-10% of the population being less than 1 nanometer and 0-10% of the population being greater than 100 nanometers.

The following detailed description should be read with reference to the drawings in which similar elements in different drawings are numbered the same. The drawings, which are not necessarily to scale, depict illustrative embodiments and are not intended to limit the scope of the disclosure.

FIG. 1 is a cross-sectional view of an embodiment of an implantable therapeutic device 100. In some embodiments, the implantable therapeutic device 100 comprises a microparticle. In some embodiments, the implantable therapeutic device 100 includes an outer portion 102 and an inner portion 104. The outer portion 102 may envelop or surround the inner portion 104. The inner portion 104 comprises magnetic nanoparticles 106 that are made of Curie materials. The term "magnetic nanoparticles" includes anti-ferromagnetic, ferromagnetic, and ferrimagnetic materials. In some embodiments, the magnetic nanoparticles 106 are formed from one or more materials such that they have a selected Curie temperature ($T_C$) between 35$^\circ$ Celsius ($^\circ$C) and 100$^\circ$C. In some embodiments, the magnetic nanoparticles have a Curie temperature of approximately 80$^\circ$C. When these magnetic nanoparticles 106 are subjected to an alternating magnetic field, the magnetic nanoparticles 106 undergo power dissipation in the form of heat caused by relaxation phenomena of the particles' magnetic moments following the electromagnetic field and the mechanical rotation of particles themselves within the dispersant medium. At temperatures less than the Curie temperature ($T<T_C$), the magnetic nanoparticles 106 are ferro- (or ferri-
magnetic, whereas the nanoparticles 106 transition into a paramagnetic phase to stabilize the nanoparticle 106 temperature at the predetermined Curie temperature.

In some embodiments, the magnetic nanoparticles 106 are made of one or more Curie materials having a predetermined composition that has a Curie temperature greater than 45 °C. Such Curie materials may be used to heat undesirable tissues up to the pain threshold of a patient, or beyond if pain mitigation drugs and/or anesthetic is used, for example. Examples of such compositions of Curie materials include Fe 70% Ni 30%, having a Curie temperature of 82°C; Fe 75% Ni 25% with 1 wt. % Mn, having a Curie temperature of 78°C. In some embodiments, the magnetic nanoparticles 106 comprise Curie materials of a predetermined composition having a Curie temperature from 42°C to 48°C, for example Manganese Arsenide having a Curie Temperature of 45°C. Other suitable Curie materials are disclosed in the concurrently filed application titled, "MEDICAL DEVICES FOR THERAPEUTIC HEAT TREATMENTS", U.S. Pat. App. Ser. No. 61/980,952 (Sutermeister et al), filed on April 17, 2014, which is herein incorporated by reference. Additionally, the contents of the co-filed Application entitled, "COMPOSITIONS FOR THERAPEUTIC HEAT DELIVERY", U.S. Pat. App. Ser. No. 61/981,003 (Sutermeister et al), also filed on April 17, 2014, are herein incorporated by reference.

In one or more embodiments, the Curie temperature material includes a zinc oxide mixed (e.g., combined, doped, etc.) with a rare earth element (e.g., a Lanthanum metal, etc.). In some embodiments, the rare earth element is present in a non-zero quantity. For example, the Curie temperature material including zinc oxide may include at least five (e.g., at least 6, at least 7, at least 8, at least 9, at least 10, at least 15) weight percent of a rare earth element, based on the sum of the weight of the rare earth element and the weight of the zinc oxide. In one or more embodiments in which the Curie temperature material includes zinc oxide and more than one rare earth element, then the sum of the rare earth element weight percentage may be at least five (e.g., at least 6, at least 7, at least 8, at least 9, at least 10, at least 15) weight percent, based on the sum of the weight of the more than one rare earth elements and the weight of the zinc oxide.

In one or more embodiments, the Curie temperature material includes gallium, manganese, and nitrogen (e.g., gallium manganese nitride, etc.). In one or more embodiments, the Curie temperature material includes gallium, manganese, and
oxygen (e.g., gallium manganese oxide). In one or more embodiments, the Curie
temperature material includes gadolinium, manganese, and nitrogen (e.g., gadolinium
manganese nitride). In one or more embodiments, the Curie temperature material
includes one or more of gallium arsenide, dysprosium, cobalt, magnetite, and
neodymium.

In one or more embodiments, the Curie temperature material may include a
magnetic nanoparticle of the composition disclosed by Kim et al. (European Pat. Publ.
No. EP 2 671 570 A2, entitled "Magnetic Nanoparticle, Having A Curie Temperature
Which Is Within Biocompatible Temperature Range, And Method For Preparing
Same"). The magnetic nanoparticle disclosed by Kim et al. includes a rare earth
metal, a divalent metal and a transition metal oxide and has a Curie temperature in the
range of -80 °C to about 41 °C. In the present disclosure, a composition may include
any of the Curie materials disclosed by Kim et al. (European Pat. Publ. No. EP 2 671
570 A2) with a polymeric binder and a thermal interface material wherein the Curie
temperature of the composition is in the range of about 17 degrees Celsius to about
400 degrees Celsius. Such magnetic nanoparticles may be formed by the methods
disclosed in Kim et al. (European Pat. Publ. No. EP 2 671 570 A2).

In one or more embodiments, the Curie temperature material includes at least
one element selected from iron (Tc = 770 °C), nickel (Tc = 354 °C), zinc (Tc = 415
°C), cobalt (Tc = 1115 °C), gadolinium (Tc = 20 °C), chromium, manganese, copper,
gallium, yttrium, aluminum, silver, and/or their alloys. In one or more embodiments,
a Curie temperature material may include boron (B), bismuth (Bi), antimony (Sb),
ar senic (As), carbon (C), silicon (Si), sulfur (S), selenium (Se), tellurium (Te),
germanium (Ge), cerium (Ce), neodymium (Nd), erbium (Er), holmium (Ho),
strontium (Sr), titanium (Ti), calcium (Ca), lanthanum (La), and/or oxygen (O).

In one or more embodiments, the Curie material includes an iron-cobalt-
chromium compound such as, for example, (Fe65Co35)7iCri8ZnB4, (having a Curie
temperature of 74.5 °C), which may be suitable in heat delivery applications including
ablation of biological tissue. Methods of forming (Fe65Co35)7iCri8ZnB4, and
ferrofluids thereof, and heat testing such materials are described by Miller et al. (See
Miller et al, "Fe-Co-Cr nanocomposites for application in self-regulated rf heating," J.
Applied Phys., 2010, 107, 09A313-1 to 09A313-3.) For example: "Ferrofluids of
varying [magnetic nanoparticle] concentration were rf heated by applying a 27.2 mT
ac magnetic field at 267 kHz. Temperature change was measured as a function of
exposure time in the cryomilled Fe-Co-Cr ferrofluids using a Luxtron optical fiber temperature probe. Using a 1.24 vol % concentration of (Fe65Co35)7iCrizZr7B4 [magnetic nanoparticles] in 10 ml of 0.150 M Pluronic F127 ferrofluid, the solution was effectively heated to reach temperatures >50 °C in -70 [seconds], while demonstrating Curie-limiting self-regulating behavior was demonstrated -74.5 °C []."

In one or more embodiments, the Curie material includes a material having the formula Fe73.5-xCr Si3.5CuiB9M>3 (x = 0 to 10), which may be amorphous or crystalline, or may be a combination of amorphous and crystalline phases. For example, Gomez-Polo has reported preparing Fe73.5-xCr Si3.5CuiB9M>3 (x = 3, 7, and 10) with and without crystallization and magnetic characterization thereof. (See Gomez-Polo et al, "Analysis of heating effects (magnetic hyperthermia) in FeCrSiBCuNb amorphous and nanocrystalline wires," J. Applied Phys., 2012, 111. 07A314-1 to 07A314-3.)

In one or more embodiments, a Curie temperature material includes an antiperovskite compound. For example, antiperovskite compounds having the formula Gai-xCMm+x, wherein x=0, 0.06, 0.07, and 0.08 are described by Wang et al, "Reversible room-temperature magnetocaloric effect with large temperature span in antiperovskite compounds Gai-xCMm+x (x=0, 0.06, 0.07, and 0.08)," J. Appl. Phys., 2009, 105, 083907-1 to 083907-5. At page 083904-2, Wang et al. reported an experimental procedure for making the compounds and reported that the Curie temperatures of such compounds, determined from the derivative of magnetism as a function of temperature curves, were found to be 250, 281.5, 296.5, and 323.5 K for x=0, 0.06, 0.07, and 0.08, respectively. In the present disclosure, in one or more embodiments in which the Curie material has the formula Gai-xCMm+x, the value for x may be any value from 0 to 0.08, or even greater than 0.08.

In one or more embodiments, a suitable Curie temperature material includes one or more of YMns (having a Curie temperature of 216 °C), Ni (having a Curie temperature of 357 °C), Gd (having a Curie temperature of 19 °C), MnBi (having a Curie temperature of 358 °C), MnSb (having a Curie temperature of 314 °C), CrO2 (having a Curie temperature of 112 °C), MnAs (having a Curie temperature of 45 °C), MnOFe203 (having a Curie temperature of 300 °C), Y3FesO12 (having a Curie temperature of 287 °C), chromium (having a Curie temperature of 113 °C), lanthanum strontium manganite (LSM) (having a Curie temperature of 75 °C), as well as combinations of these.
Suitable Curie temperature materials are also disclosed by Haik et al. (U.S. Pat. No. 7,842,281; "Magnetic Particle Composition for Therapeutic Hyperthermia") such as essentially any composition that has a desired Curie temperature and that can be effectively heated by application of a magnetic field, such as iron, nickel, zinc, cobalt, gadolinium, chromium, manganese, and/or their alloys, an alloy of copper and nickel, an alloy of 71 to 71.4 wt % nickel with the balance consisting essentially of copper, an alloy of 71 wt % nickel and 29 wt % copper, a Mn—Zn ferrite having the formula Zn$_x$Mn$_{1-x}$Fe$_{20}$ where $x$ is between 0.6 and 0.8, a Gd-substituted Mn—Zn ferrite, a ferrite having the formula Mn$_{0.5}$Zn$_{0.5}$Gd$_{0.02}$Fe$_{20}$ where $x$ is between 0 and 1.5, an iron compound having a composition of Fe$_{1-x}$Zn$_x$Fe$_{20}$ where $x$ is between 0.7 and 0.9, ZnFe$_{20}$, and ZnGd$_3$Fe$_{20}$ where $x$ is between 0.01 and 0.8. See Haik et al. (U.S. Pat. No. 7,842,281) at column 5, lines 10-33. Methods of making such materials are also disclosed by Haik et al. (U.S. Pat. No. 7,842,281) at column 6, line 53 to column 9, line 11 and in the Examples at column 10, line 45 to column 17, line 14.

In one or more embodiments, the Curie material includes an iron-nickel compound (e.g., Fe$_7$O$_3$Ni$_3$) that may or may not include chromium. In one or more embodiments, a Curie temperature material includes an iron-nickel alloy having the formula Fe$_{3}$Ni$_{1-x}$, wherein $x$ is from 0.10 to 0.40 (e.g., $x$ may be 0.12, 0.14, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, etc.). In one or more embodiments, Fe$_{3}$Ni$_{1-x}$ may have manganese added thereto (e.g., 1 wt % Mn added to Fe$_{3}$Ni$_{1-x}$, such as when $x=0.25$).

McNerny et al. describe chemical synthesis of monodisperse Fe-Ni magnetic nanoparticles with tunable Curie temperatures. (See McNerny et al., "Chemical synthesis of monodisperse $\gamma$-Fe-Ni magnetic nanoparticles with tunable Curie temperatures for self-regulated hyperthermia," J. Applied Phys., 2010, 107, 09A3 12-1 to 09A3 12-3.) For example, McNerny reported that Fe$_{0.7}$O$_{3}$Ni$_{0.3}$ magnetic nanoparticles have a Curie temperature of about 82 °C, a temperature that may be useful for heat delivery (e.g., medical applications involving ablation, etc.). In another example, McNerny reported that 1 weight percent of manganese added to Fe$_{0.7}$O$_{3}$Ni$_{0.25}$ has a Curie temperature of about 78 °C.

In the present disclosure, a Curie temperature material may have a Curie temperature in the range of 40 °C to 80 °C. For example, Martirosyan has reported a number of Curie temperature materials having a Curie temperature in the range of about 45 °C to about 50 °C. (See Martirosyan, "Thermosensitive Magnetic
Nanoparticles for Self-Controlled Hyperthermia Cancer Treatment," J. Nanomed. Nanotechnol, 2012, 3(6): 1000el 12-1.) For example, Martirosyan has disclosed ultrafine alumina coated particles of substituted ferrite Coi- Zn,Fe20 4 and yttrium-iron garnet Y3Fe5-xAlxO12 having a Curie temperature of about 50°C (citing Prasad et al. "Gd

"Investigation on Tc tuned nano particles of magnetic oxides for hyperthermia applications," Biomed. Mater. Eng., 2003, 13: 387-399); copper nickel (CuNi) alloy nanoparticles with varying Curie temperature from 40 to 60°C, synthesized by several techniques (citing Kuznetsov et al, "Local radiofrequency-induced hyperthermia using CuNi nanoparticles with therapeutically suitable Curie temperature," J. Magn. Magn. Mater., 2007, 311: 197-203); Nickel-Chromium (Nii-xCrx) particles having a Curie temperature in range of 43-44 °C, the Curie temperatures of the alloys decreasing almost linearly with increasing chromium concentration from 4.5 to 5.9 wt % (citing Akin et al., "Nii-xCrx alloy for self controlled magnetic hyperthermia," Crystal Research and Technology, 2009, 44: 386-390); Gd$_3$(Si$_{1-x}$Ge$_x$)$_4$ and (Gd$_{1-x}$R$_x$)$_5$Si$_4$ series, with R = Ce, Nd, Er, and Ho, have been studied (citing Ahmad et al, "Optimization of (Gd)$_3$Si$_4$ based materials: A step toward self-controlled hyperthermia applications," J. Appl. Phys., 2009, 106: 064701); ferromagnetic La$_{0.75}$Sr$_{0.25}$MnO$_3$ nanoparticles (particle size of 20-100 nm) having a Curie temperature of about 45 °C (citing Prasad et al. "TC-Tuned biocompatible suspension of La$_{0.75}$Sr$_{0.25}$MnO$_3$ for magnetic hyperthermia," J. Biomed. Mater. Res. B Appl. Biomater., 2008, 85: 409-416); unaggregated La$_{0.82}$Sr$_{0.18}$MnO$_3$+6 perovskite nanoparticles with a mean crystallite size of 22 nm having a Curie temperature of about 43 °C; complex ferrite nanoparticles with formula Mg$_{1-x}$Fe$_{2-x}$Ti$_x$O$_{4}$ (where 0<x<0.5) having a Curie temperatures in the range of about 45-50 °C (citing Shimizu et al, "Ferromagnetic exchange interaction and Curie temperature of Mg$_{1-x}$Fe$_{2-x}$Ti$_x$O$_{4}$ (x=0-0.5) system," J. Magn. Magn. Mater., 2007, 310:1835-1837) and Martirosyan, "Thermosensitive nanostructured media for imaging and hyperthermia cancer treatment," Bulletin of the American Physical Society, 2001, 56:1); Zn-doped Mn-ferrite, Mn$_{1-x}$Zn$_x$O and the Gd-doped Zn-ferrite, ZnGd$_x$Fe$_{2-x}$O$_4$ nanoparticles having Curie temperatures tuned to about 43 °C; and magnetic nanocomposite Ni$_2$Co$_8$Gd$_{0.08}$Fe$_{1.92}$O$_4$ encapsulated by poly vinyl alcohol and synthesized by a two steps chemical reaction including solgel combustion and solvent casting technique also can be applicable for self controlled hyperthermia (citing Prasad et al. "Gd

In one or more embodiments, a Curie temperature material may include a rare-
earth manganite material. In one or more embodiments, the Curie material includes a
lanthanum oxide compound (e.g., La$_{0.8}$Ag$_{0.2}$MnO$_{3}$, La$_{0.75}$Sr$_{0.25}$MnO$_{3}$, Lao.8Sro.2Mn03, etc.). For example, Lai$_{x}$Sr$_{y}$Mn03-δ (LSMO) and Lai$_{x}$Ag$_{y}$Mn03-δ (LAMO) may be useful. In one or more embodiments wherein a Curie temperature
material includes Lai$_{x}$Ag$_{y}$Mn03-δ (LSMO), x may be 0.01 to 0.30 (e.g., 0.20), y may be 0.01 to 0.30 (e.g., 0.15), and δ may be 0.00 to 0.10 (e.g., 0.05) (e.g.,
Lao.8Ag0.2MnO2.95, which has been reported as having a Curie temperature in the
range of about 42-44 °C). (See Atsarkin et al, "Solution to the bioheat equation for
hyperthermia with Lai$_{x}$Ag$_{y}$Mn03-d nanoparticles: The effect of temperature autostabilization," Int. J. Hyperthermia, 2009 May; 25(3):240-247.) In one or more
embodiments wherein a Curie temperature material includes Lai$_{x}$Sr$_{y}$Mn03-δ (LSMO),
x may be 0.01 to 0.30 (e.g., 0.05, 0.10, 0.15, 0.20, 0.25) and δ may be 0.00 to 0.10
(e.g., 0.00) (e.g., Lao.75Sr0.5Mn03 (having a Curie temperature of about 56°C), Lao.8Sro.2Mn03 (having a Curie temperature of about 48°C), Lao.85Sro.isMn03, etc.).
In one or more embodiments, a composition having a Curie temperature of about 42
°C may be useful in one or more heat delivery applications (e.g., hyperthermia
treatment of biological tissue wherein heat is to be delivered while reducing or
avoiding undue thermal damage to the surrounding tissue).

In one or more embodiments, a Curie temperature material includes a
chromium arsenic alloy, such as CrAs, CrAssoSso, CrAssoSbso, CrAssoSeso,
CrAssoTeso.

In one or more embodiments, the composition includes a Curie temperature
material and a secondary material. In one or more embodiments, the secondary
material may include a metal (e.g., an elemental metal, a metal oxide, a metal salt, an
alloy, etc.) that is different from the Curie temperature material. In some
embodiments, the secondary material may be one metal or may be an alloy of two or
more metals. In one or more embodiments, the secondary material may include a
small amount of one or more non-metals (e.g., less than five percent by weight based
on the combined weight of the Curie temperature material and the one or more non-
metals). In the present disclosure, a secondary material may include an alloy such as,
for example, an iron-nickel alloy, a nickel-copper alloy, an iron-nickel-chromium
alloy, or the like. In the present disclosure, the secondary material includes, but is not
limited to, iron, cobalt, nickel, gadolinium, dysprosium, MnBi, MnSb, Cr0 2, MnAs,
EuO, Fe20 3, FeOFe 20 3, NiOFe 20 3, CuOFe 20 3, MgOFe 20 3, MnOFe 20 3, Y3Fe0 12,
chromium, lanthanum strontium manganite, YMns, silicon, aluminum, manganese,
ZnO, and GaMnN.

In one or more embodiments, the Curie temperature material and the secondary material may form a homogenous mixture. Alternatively, the Curie temperature material and the secondary material may be mixed (e.g., combined, doped, etc.) to form a heterogeneous mixture.

In one or more embodiments, the composition includes a mixture that includes first Curie temperature material and a second Curie temperature material that is different from the first Curie temperature material. In some embodiments, a third Curie temperature material may be included in the composition with the first and second Curie temperature materials. Suitable materials for each of the first, second, and third Curie temperature materials include any Curie temperature material including, but not limited to, the Curie temperature materials disclosed herein. In one or more embodiments, a mixture of one or more Curie temperature materials exhibits a Curie temperature in a range of about 38 degrees Celsius to about 45 degrees Celsius or in a range of about 55 degrees Celsius to about 95 degrees Celsius. In some embodiments, a mixture of first and second Curie temperature materials includes an alloy of the first and second Curie temperature materials (e.g., first and second metallic Curie temperature materials, etc.). In some embodiments, a mixture of first and second Curie temperature materials includes a first Curie temperature material doped with a second Curie temperature material. In one or more embodiments, a mixture of first and second Curie temperature materials includes a nanocomposite (e.g., a composite of two materials in the form of a nanoparticle, etc.) of the first and second Curie temperature materials.

In one or more applications of heat delivery (e.g., therapeutic heat delivery), a particular Curie temperature or a range of Curie temperatures may be desired. In the present disclosure, it is contemplated that a composition may be selected (e.g., formulated, etc.) with a target Curie temperature (or range of Curie temperatures) to provide a desired temperature treatment to a subject (e.g., the object to be heat treated, tissue to be heat treated, etc.). It should be recognized that one of skill in the art may select a Curie temperature material having a Curie temperature and may tune that
Curie temperature by, for example, modifying chemical composition (e.g., mixing, doping, etc.), modifying shape (e.g., providing spherical particles, providing nonspherical particles), modifying particle size, and/or modifying domain control of the composition to reach a desired temperature of heat delivery.

For example, particle size in a crystal lattice changes Curie temperature. Although not wishing to be bound by theory, as particle size decreases, the fluctuations in electron spins becomes more significant, causing disorder in magnetic moments and lowering Curie temperature. For example, in superparamagnetism, magnetic moments change randomly, creating disorder in small ferromagnetic particles. For example, in some instances, by reducing the particle size to the nanometer scale, the specific absorption rate, or magnetic absorbance, may be increased by a factor of around 10.

Although not wishing to be bound by theory, Curie temperature of nanoparticles are also affected by the crystal lattice structure, body-centered cubic (bcc), face-centered cubic (fee) and a hexagonal structure (hep) all have different Curie Temperatures due to magnetic moments reacting to their neighboring electron spins. For example, tighter lattice structures (e.g., fee and hep) have higher Curie temperatures than other lattice structures (e.g., bcc) as the magnetic moments have stronger effects when closer together. In smaller systems, the coordination number for the surface may be more significant and the magnetic moments may have a stronger effect on the system.

In some embodiments, a composition that includes a secondary material (e.g., a second Curie temperature material different from a first Curie temperature material) may have a Curie temperature that is reduced as compared to the composition without (e.g., in the absence of) that secondary material. In one or more embodiments, in some combinations of two or more Curie materials (e.g., each having greater than 10% by weight), the combined material has a Curie temperature that is reduced as compared to either individual material. For example, each of iron and nickel has a higher Curie temperature than that of at least some iron-nickel alloy compositions.

For example, although the Curie temperature of iron is about 770 °C and the Curie temperature of nickel is about 354 °C, an alloy of Fe$_6$Ni$_4$ has a Curie temperature of about 300 °C. In one or more embodiments, alloying a given Curie temperature material with an element such as silicon (Si), Aluminum (Al), or manganese (Mn)
may result in a mixture having a Curie temperature that is reduced as compared to the
given Curie temperature material.

In one or more embodiments, the composition may include a secondary
material that is a non-Curie temperature material (e.g., not having a Curie
temperature). In one or more embodiments, inclusion of a secondary material that is a
non-Curie temperature material in a sufficient quantity may affect (e.g., reduce or
increase) the Curie temperature of the overall composition.

In one or more embodiments, the shape of a Curie temperature material may
be selected to tune the Curie temperature of a material. For example, Iorga et al.
73(4): 195-202) disclose in Table 3 that Curie temperatures of four chemical
compositions in spherical and toroidal form can vary from about 1 to about 5 °C.
Iorga et al. found the following Curie temperatures for spherical and toroidal samples:

Cr4Ni32Fe62Mn SiO₅ (328 K vs. 330 K); Cr₄Ni₃3Fe₆2.5SiO₅ (393 K vs. 398 K);
CriiNiissFe₃₃sMnsSiO₅ (283 K vs. 285 K); CriiNi₃3Fe₅₃sSiO₅ (339 K vs. 340 K). The
results of Iorga et al. also exemplify the effect of increasing manganese content in
lowering a Curie temperature. It can also be seen that in these samples, the effect of
increasing manganese content had a greater effect than increasing chromium content.

In one or more embodiments, a Curie temperature material may include non-
zero quantities of both chromium and manganese. In at least one embodiment, the
sum of chromium and manganese may be from about 4 percent to about 13 percent
(e.g., 4-6%), based on the weight of the Curie temperature material. In some
embodiments, the inclusion of both manganese and chromium may result in a cost
savings for a given amount of Curie temperature reduction.

The impact of lattice structure and elemental spacing on Curie temperature is
disclosed by Bose et al. ("Exchange interactions and Curie temperatures in Cr-based
alloys in Zinc Blende structure: volume- and composition-dependence," arXiv:0912.1760 [cond-mat.mtrl-sci]. 5 Feb 2010; 16 pgs.) at Figs. 17-19 for Cr-
based pnictides and chalcogenides of the form CrX with X=As, Sb, S, Se and Te, and
the mixed alloys CrAssoXsO with X=Sb, S, Se, and Te. Although not wishing to be
bound by theory, the lattice spacings are generally governed by formulation,
underscoring the impact of formulation (i.e., composition) on Curie temperature.

Although not wishing to be bound by theory, generally, alignment of magnetic
moments and material density affect the bulk and surface Curie temperatures of a
given composition. The inclusion of additives impacts the lattice structure of a composition, which is important due to the impact of additives on both of these features (i.e., alignment of magnetic moments and density of the composition). For example, a decrease in alignment of magnetic moments decreases the overall magnetism of the bulk material, thus generally lowering the Curie temperature. In another example, a decrease in the density of Curie temperature materials within a composition serves to separate magnetic moments, thus generally lowering Curie temperature.

In the present disclosure, altering the alignment of magnetic moments may be accomplished with any of a wide variety of different binders (e.g., a polymeric binder, a non-polymeric binder that includes a metal or a ceramic, etc.). Although not wishing to be bound by theory, within a small Curie temperature element (e.g., having a dimension in the nano and/or micro scale), the shift in alignment is primarily a function of lattice structure, however grain boundaries may play a role (much more common in larger bulk structures). In some embodiments, a nanocomposite material may include high and low bulk Curie temperatures, but will exhibit only one mean-field Curie temperature. Generally, a higher proportion of lower bulk temperatures results in a lower mean-field Curie temperature. In the present disclosure, by forming a composition including a Curie temperature material and a binder (e.g., polymer, non-polymer, ceramic, non-Curie temperature metallic material, etc.) a Curie temperature material’s magnetism is reduced, lowering the Curie temperature.

In some embodiments, the outer portion 102 comprises radiopaque particles 108 residing outside the inner portion 104. As shown, the outer portion 102 may enclose radiopaque particles 108 which, in some embodiments, are made of gold. Other examples of materials for such radiopaque particles 108 include, but not limited to, titanium dioxide, bismuth subcarbonate, platinum and barium sulfate, platinum iridium, platinum tungsten, or any other suitable alloy of platinum, palladium, or gold. The radiopaque particles may allow for the detection of the exact distribution (and, as such, density) of magnetic nanoparticles 106 in or adjacent to undesirable tissue or tumor, using a variety of techniques. For example, a computerized tomography (CT) scan of a portion of the patient’s body may be used to view where the magnetic nanoparticles 106 are released or injected. In some embodiments, the radiopaque particles 108 are nanoparticles.
In some embodiments, the outer portion 102 includes a therapeutic drug in lieu of or in addition to the radiopaque particles 108. The terms "therapeutic agents," "drugs," "bioactive agents," "pharmaceuticals," "pharmaceutically active agents", and other related terms may be used interchangeably herein and include genetic therapeutic agents, non-genetic therapeutic agents, and cells. Therapeutic agents may be used singly or in combination. A wide range of therapeutic agent loadings can be used in conjunction with the devices of the present invention, with the pharmaceutically effective amount being readily determined by those of ordinary skill in the art and ultimately depending, for example, upon the condition to be treated, the nature of the therapeutic agent itself, the tissue into which the dosage form is introduced, and so forth.

Some specific beneficial agents include chemotherapeutic agents, anti-thrombotic agents, anti-proliferative agents, anti-inflammatory agents, anti-migratory agents, agents affecting extracellular matrix production and organization,antineoplastic agents, anti-mitotic agents, anesthetic agents, anti-coagulants, vascular cell growth promoters, vascular cell growth inhibitors, cholesterol-lowering agents, vasodilating agents, and agents that interfere with endogenous vasoactive mechanisms.

The therapeutic drug may be a chemotherapeutic agent including, but not limited to, Everolimus, platins, such as carboplatin and cisplatin, taxanes such as docetaxel and paclitaxel; gemcitabine, VP 16, mitomycin, idoxuridine, topoisomerase I inhibitors such as irinotecan, topotecan and camptothecins; nitrosoureas such as BCNU, ACNU or MCNU, methotrexate, bleomycin, adriamycin, Cytoxan and vincristine; immunomodulating cytokines such as IL2, IL6, IL12 and IL13, and interferons. Certain chemotherapeutic agents are known to be potentiated by heating the tissue and/or the chemotherapeutic agent. Examples of possible heat-activated or heat-enhanced chemotherapeutic agents include bleomycin, BCNU, cisplatin, cyclophosphamide, melphalan, mitoxantrone, mitomycin C, thiotepa, misonidazole, 5-thi-D-glucose, amphotericin B, cysteine, cysteamine, and AET.

Numerous additional therapeutic agents useful for the practice of the present invention may be selected from those described in paragraphs [0040] to [0046] of commonly assigned U.S. Patent Application Pub. No. 2003/0236514, the entire disclosure of which is hereby incorporated by reference.
In some embodiments, one or both of the outer portion 102 and the inner portion 104 is made of a variety of biocompatible thermoplastic polymers or ceramics, or any combination thereof. Examples of these biocompatible thermoplastic polymers include, but not limited to, polyglycolide (PGA), copolymers of glycolide such as glycolide/L-lactide copolymers (PGA/PLLA), glycolide/trimethylene carbonate copolymers (PGA/TMC); polylactides (PLA), stereocopolymers of PLA such as poly-L-lactide (PLLA), Poly-DL-lactide (PDLLA), L-lactide/DE-lactide copolymers; copolymers of PLA such as lactide/tetramethylene glycolide copolymers, lactide/trimethylene carbonate copolymers, lactide/5-valerolactone copolymers, lactide ε-caprolactone copolymers, polydipsipeptides, PLA/polyethylene oxide copolymers, unsymmetrically 3,6-substituted poly-l,4-dioxane-2,5-diones; poly-p-hydroxybutyrate (PHBA), PHBA/β-hydroxyvalerate copolymers (PHBA/HVA), poly-p-hydroxypropionate (PHPA), poly-p-dioxanone (PDS), poly-5-valerolactone, poly-e-caprolactone, methylethacrylate-N-vinyl pyrrolidone copolymers, polyesteramides, polyesters of oxalic acid, polydihydropyrans, polyalkyl-2-cyanoacrylates, polyurethanes (PU), polyvinyl alcohol (PVA), polypeptides, poly-p-maleic acid (PMLA), poly-p-alkanoic acids, or any combination thereof. Examples of biocompatible ceramics include, but not limited to, calcium phosphate-based ceramics such as hydroxyapatite (HAP), tricalcium phosphate β (β TCP), and a mixture of HAP and β TCP.

In some embodiments, the inner portion 104 is made of a biocompatible polymer including a polyamide. In some embodiments, the inner portion 104 is made of a biocompatible polymer including polylactic acid, poly(lactic-co-glycolic) acid (PLGA), or combinations thereof. In some embodiments, the inner portion 104 is made of a biocompatible ceramic including tri-calcium phosphate. These biocompatible polymers and ceramics may be made biodegradable for use in vivo.

In some embodiments, the inner portion 104 is coated with a biodegradable phase change material, used in conjunction with a therapeutic drug and Curie nanoparticles 106, in order to trigger drug release at a specified temperature. In some embodiments, the Curie nanoparticles 106 have a Curie temperature that is the same as or slightly above the phase change temperature of the biodegradable material. For example, in the presence of an applied electric and/or magnetic field, the Curie nanoparticles 106 may heat to their Curie temperature. Once the phase change temperature of the biodegradable material has been reached, it may soften and the
drug within the biodegradable material released. In some embodiments, the biodegradable phase change material, such as 1-tetradecanol, has a melting or phase change temperature of 39 °C, although other suitable biodegradable phase change materials, such as lauric acid, are also contemplated. In some embodiments, the inner portion 104 is made of porous PLGA particles. In some embodiments, a solution of 1-tetradecanol is prepared in di-ethyl ether and added with 10% by weight of Lanthanum Strontium Manganese Nickel Oxide (LSMNO) nanoparticles using an ultrasonic spray system. The LSMNO nanoparticles may be coated with gold for increased radiopacity of the final solution. In some embodiments, the PLGA, in the inner portion 104, is coated with gold-coated LSMNO nanoparticles, including a layer of 1-tetradecanol, using a fluidized bed system.

The implantable therapeutic device 100 can range in size from 1 micron (µm) to 30 microns, based on the intended purpose for treatment of the tissue. The implantable therapeutic device 100 can also be smaller than 1 micron and larger than 30 microns. For example, the implantable therapeutic device 100 may be sized according the location in which it is to be implanted. In some embodiments, the implantable therapeutic device 100 may be injected, or otherwise implanted, into the body to occlude the vascular bed of the undesirable tissue due to its predetermined size in the given size range. Such implantable therapeutic devices 100 may function to block the oxygen supply, in addition to delivering heat and/or a therapeutic drug, to the tissue for treatment. In other embodiments, the implantable therapeutic device 100 may be injected, or otherwise implanted, into the body or bulk of the tumor or undesirable tissue.

Once implanted, the therapeutic device 100 may be subjected to an alternating electric or magnetic field. The electric or magnetic field may be applied from a location external to the body and directed at the location of the therapeutic device(s) 100. When subjected to a field of sufficient intensity, the metallic nanoparticles 106 heat up to a characteristic temperature at which their magnetic properties switch to paramagnetic properties and at which the temperature of the Curie temperature material stops increasing. The heat generated by the metallic nanoparticles 106 may trigger a release of a therapeutic drug and/or heat the surrounding tissue to provide hyperthermic treatment. It is further contemplated that the implantable therapeutic device 100 could act as a temperature catalyst for another reaction in which a reaction or an activity is dormant until heat activated. The device 100 heats only in the
presence of a specified electric or magnetic field and frequency and only to the Curie temperature of the nanoparticles 106. When the Curie temperature is reached, the material goes from magnetic to non-magnetic, discontinuing the heating. This is a cyclic process that permanently and rapidly maintains the therapeutic device 100 temperature at the set Curie point of the material, as long as the electric or magnetic field is applied.

FIGs. 2A and 2B are cross-sectional views of an embodiment of an implantable therapeutic device 200 in a closed configuration and an open configuration, respectively. In some embodiments, the implantable therapeutic device 200 includes a metallic or metal composite shell 202 made up of one or more Curie materials having a predefined Curie temperature. The size of the implantable therapeutic device 200 may range from 1 micron to 3000 microns. In some embodiments, however, the implantable therapeutic device 200 comprises a microparticle, ranging in size from 1 micron to 1000 microns. For example, the implantable therapeutic device 200 may be sized according the location in which it is to be implanted.

As shown in FIG. 2A, the metallic shell 202 includes a cavity 205 having a first portion 204 and a second portion 206, the second portion 206 extending from the first portion 204 to the outer surface 207 of the metallic shell 202. In some embodiments, the first portion 204 is substantially larger than the second portion 206, which is relatively small, although this is not required. Further, in some embodiments, the first portion 204 is located at or near the center of the metallic shell 202. Further still, in some embodiments, one or both of the first and the second portions 204, 206 comprise a biocompatible thermoplastic polymer and/or biocompatible ceramic 208, having a drug 210 or radiopaque material, or both. Alternatively, the first and the second portions 204, 206 may include suitable different and/or separate biocompatible thermoplastic polymers and/or biocompatible ceramics. In some embodiments, the second portion 206 is sealed by the thermoplastic polymer or ceramic 208 prior to release of the biocompatible thermoplastic polymer and/or biocompatible ceramic and drug 210. For example an electric or magnetic field may be applied to the implantable therapeutic device 200 causing the metallic shell 202 to heat to its Curie temperature. The heat from the metallic shell 202 may be passed to the thermoplastic polymer or ceramic 208, causing the thermoplastic polymer or ceramic 208 to soften and/or melt and release the drug 210. In order to release the
drug 210, the thermoplastic polymer/ceramic 208 may have a melting temperature below the Curie temperature of the metallic shell 202.

In some embodiments, the implantable therapeutic device 200 is formed using a porous metallic microparticle (e.g., formed by sintering nanoparticles or smaller micro-particles together). The porous metallic microparticle is dipped into a solution of the drug and a dissolvable wax. In some embodiments, the porous metallic microparticles are formed by mixing 2 micrometer iron particles into a polymer solution (e.g., 50% polymer by weight), and spraying, out of the solution, microparticles being approximately 100 micrometers in size. Then, the resulting microparticles (at this stage containing iron particles and polymer) are sintered to burn off the polymer, leaving behind porous metallic microparticles, to which the drug and wax can be added.

As shown in FIG. 2B, the metallic shell 202 is heated (shown at reference number 209) to a temperature T1 under the influence of an applied alternating magnetic or electric field. At temperature T1, the thermoplastic polymer/ceramic 208 weakens, loosens, softens and/or melts to open a path 211 for the drug 210 and/or radiopaque particles to flow out from the metallic shell 202 into the body lumen or body tissue. The thermoplastic polymer/ceramic 208 may weaken, loosen, soften and/or melt at a temperature T1 below the Curie temperature of the metallic sheet 202, although this is not required. In some embodiments, or in some methods of treatment, once the drug 210 is released, the intensity of the applied magnetic field or electric field may be increased to further raise the temperature of the metallic shell 202 near or to its Curie temperature. As a result, localized thermal therapy or cauterization of undesirable tissue can be undertaken in addition to the drug therapy from the released drug 210. However, the metallic shell 202 does not heat above its Curie temperature.

FIGs. 3Aand 3B are cross-sectional views of an embodiment of an implantable therapeutic device 300 which, in some embodiments, comprises a microparticle. FIG. 3A shows the implantable therapeutic device 300 in a closed configuration, while FIG. 3B shows the implantable therapeutic device in an open configuration. In some embodiments, the implantable therapeutic device 300 includes a metallic or metal composite core 302 comprising a Curie material having a predefined Curie temperature. The size of the implantable therapeutic device 300 may range from 1 micron to 3000 microns; where the implantable therapeutic device is a microparticle,
it may range in size from 1 micron to 1000 microns. For example, the implantable therapeutic device 200 may be sized according the location in which it is to be implanted.

As shown in FIG. 3A, the outer surface 303 of the metallic core 302 is covered with a therapeutic drug 304, examples of which are discussed above, and/or radiopaque particles. The metallic core 302 and the therapeutic drug 304 are enclosed within or surrounded by a suitable biocompatible thermoplastic polymer and/or biocompatible ceramic 306. The melting temperature of the thermoplastic polymer or biocompatible ceramic 306 may be less than or approximately equal to the Curie temperature of the metallic core 302. When the implantable therapeutic device 300 is subjected to an appropriate alternating magnetic or electric field, the metallic core 302 begins to heat. The temperature of the metallic core 302 may be limited, however, upon reaching the Curie temperature, as the metallic core 302 becomes paramagnetic.

In some embodiments, the melting temperature of the biocompatible thermoplastic polymer and/or biocompatible ceramic 306 is at or slightly below the Curie temperature of the metallic core 302. In some embodiments, however, the melting temperature of the biocompatible thermoplastic polymer and/or biocompatible ceramic 306 is significantly below the Curie temperature of the metallic core 302. An electric or magnetic field may be applied to the implantable therapeutic device 300 causing the metallic shell 302 to heat to or towards its Curie temperature. The heat from the metallic shell 302 may be passed to the thermoplastic polymer or ceramic 308, causing the thermoplastic polymer or ceramic 308 to soften and/or melt and release the drug 304. In this way, once the drug 304 is released, intensity of the applied magnetic or electric field may be increased to further raise the temperature of the metallic core 302 near or to its Curie temperature. As a result, the metallic core 302 can further be used for localized thermal therapy or cauterization of undesirable tissue after deployment of a therapeutic drug 304. Heating ceases once the temperature of the metallic core 302 reaches its Curie temperature.

In some embodiments, a first portion of the metallic core 302 is surrounded by a first thermoplastic polymer and/or ceramic, and a second portion of the metallic core 302, along with the drug 304, is surrounded by a second thermoplastic polymer and/or ceramic. The melting temperature of the second thermoplastic polymer/ceramic may be greater than the melting temperature of the first thermoplastic polymer/ceramic but less than the Curie temperature of the metallic core 302. As a result, when subjected
to an alternating magnetic or electric field, the heat dissipated by the metallic core 302 breaks the first thermoplastic polymer first followed by breaking of the second thermoplastic polymer, thereby releasing the drug 304 in parts. It is contemplated that the drug 304 may be disposed under one or both the first and second thermoplastic polymer and/or ceramic. It is further contemplated that the implantable therapeutic device 300 may include any number of thermoplastic polymers and/or ceramics desired, such as, but not limited to, one, two, three, four, or more.

FIG. 4 illustrates a schematic of an embodiment of an implantable therapeutic device 400 which, in some embodiments, comprises a microparticle. The implantable therapeutic device 400 includes a base 402 having a sharp edge 404 protruding outwards from the outer surface 403 of the base 402. The sharp edge 404 may be configured to cauterize or cut undesirable tissue. The base 402 may be a metal or metal composite made up of one or more Curie materials having a predefined Curie temperature. In some embodiments, the base 402 may be substantially spherical. The base 402 can also take on any other desirable form, such as, but not limited to a ring. In some embodiments, the base 402 and the sharp edge 404 may be made from one or more suitable Curie materials having the same or different Curie temperatures. Under the influence of an alternating magnetic or electric field, the base 402 and/or the sharp edge 404 can be raised to the Curie temperature, as previously discussed, in order to cauterize the surrounding tissue. In some embodiments, the base 402 and/or sharp edge 404 have a Curie temperature between 100 and 400 degrees Celsius.

With regard to FIG. 5, in some embodiments, an implantable therapeutic device 500 comprises a portion 502 made up of one or more Curie materials having a predetermined Curie temperature. In some embodiments, the implantable therapeutic device comprises a microparticle. In some embodiments, the portion 502 has a through hole 504 extending through the device 500 to receive a guidewire for delivery. The hole 504 may be located at about the center of the portion 502, but may also be located at any suitable location on the portion 502. Under the influence of an alternating magnetic or electric field, the metallic portion 502 dissipates heat to the surrounding tissue. The implantable therapeutic devices 400 and 500 may have variable sizes ranging from 1 micron to 3000 microns based on the intended purpose for treatment of the undesirable tissue, as discussed above.

FIGs. 6, 7, and 8 are schematic illustrations of catheters for delivering the implantable therapeutic devices. As illustrated, the catheters 600, 700, 800 are
configured to navigate through a patient's vasculature to a desired treatment site.
Each of the catheters 600, 700, 800 comprises a catheter shaft 601. The catheter shaft 601 has a distal end portion 602. The proximal end of each of the catheters 600, 700, 800 may include a hub (not shown) attached thereto for connecting other diagnostic and/or treatment devices and/or a port for facilitating interventions. In addition, the catheters 600, 700, 800 have a cross-sectional shape or configuration adapted to be received in a desired body lumen. For instance, the catheters 600, 700, 800 may be specially sized and configured to accommodate passage through the intravascular path, which leads from a percutaneous access site in, for example, the femoral, brachial, or radial artery, to a targeted treatment site, for example, within the stomach or other organ of a patient.

The stiffness of the catheters 600, 700, 800 may be set for use in various body lumen diameters. To this end, the material used for manufacturing the catheters 600, 700, 800 may include any suitable biocompatible material such as, but are not limited to, polymers, or alloys, either in combination or alone. In general, suitable polymeric materials include, but are not limited to, silicone, polyamide, polyether block amides, polyurethane, polyethylene, nylon, and polyethylene terephthalate. In some embodiments, the material employed has enough stiffness for use in various body lumen diameters, and sufficient flexibility to maneuver through tortuous and/or stenotic lumens, avoiding any undesirable tissue injuries. It will be appreciated that delivery devices can include cutting, cauterizing, and/or piercing capabilities for the purpose of deploying the implantable therapeutic devices in non-luminal target locations, as well.

FIG. 6 illustrates a catheter 600 for delivering one or more implantable therapeutic devices to body tissue using a fluid, which can be pressurized to deliver the implantable therapeutic devices. The catheter 600 may include a lumen 603 extending from the distal end portion 602 towards the proximal end portion. The distal end portion 602 of the catheter shaft 601 comprises an elastic orifice 604 that is capable of transitioning between a closed configuration and an open configuration. The orifice 604 may be biased towards the closed configuration. An applied force may cause the orifice 604 to move between the closed configuration and the open configuration.

In some embodiments, the catheter 600 comprises a handle portion 607. The handle portion 607 has a reservoir 608 which is in fluid communication with the
lumen 603. Within the reservoir 608 is a fluid 609. In some embodiments, the reservoir 608 comprises a syringe in fluid communication with the lumen 603 and elastic orifice 604. The cross-sectional diameter of the lumen 603 is sized to receive one or more implantable therapeutic devices, for example microparticles such as, but not limited to the therapeutic device 100 discussed above. While the catheter 600 is described with respect to the implantable therapeutic device 100 described with respect to Figure 1, it is contemplated that any of the implantable therapeutic devices 100, 200, 300, 400, 500 described herein can be delivered with the catheter 100. The elastic orifice 604 may be biased towards the closed configuration when the implantable therapeutic device 100 is within the lumen of the catheter 600.

In some embodiments, the catheter 600 comprises a precision volume pump 606 and a reservoir 608 that stores the fluid 609, for example, saline or any other suitable biocompatible fluid. In some embodiments, the reservoir 608 is coupled to the lumen such that when the pump 606 is activated, the fluid 609 flows into the lumen, pushing the implantable therapeutic device 100, distally. The pressure from the fluid 609 and the distally advancing therapeutic device may apply a force to the orifice 604 causing the orifice to open. The pushed implantable therapeutic device 100 may flow out from the elastic orifice 604, which transitions from the closed configuration to the open configuration to release the implantable therapeutic device 100 into a body lumen or tissue. In some embodiments, the stored potential energy of the elastic orifice 604 in the closed configuration converts into kinetic energy in the open configuration to additionally apply a distal force on the microparticle 100. In some embodiments, the applied force drives the implantable therapeutic device 100 into the body lumen or tissue.

FIG. 7 illustrates a catheter 700 configured to deliver an implantable therapeutic device over a guidewire 610 to body tissue. The catheter 700 is configured to receive one or more implantable therapeutic devices such as, but not limited to, the implantable therapeutic device 500 described with respect to FIG. 5, which can be mounted over the guidewire 610. The catheter 700 includes a first lumen 611 extending between a proximal opening at the proximal end 620 and a distal opening 622 at the distal end 624. The cross-sectional diameter of the first lumen 611 is sufficient to receive the implantable therapeutic device 500 mounted over the guidewire 610. At the proximal end, the catheter 700 has a push shaft 612 surrounding the guidewire 610. The push shaft 612 may be extended or advanced
distally over the guidewire 610 to mechanically push the implantable therapeutic
devices 500 distally off of the guidewire and into a body lumen or tissue.

FIG. 8 illustrates a catheter 800 for fusible release of implantable therapeutic
devices, such as, but not limited to, the implantable therapeutic device 500 described
with respect to FIG. 5 mounted over a fusible link 614 using electrical discharge or
releasable mechanical interlock. As shown, the catheter 800 is configured to receive a
plurality of implantable therapeutic devices 500, such as a microparticle, mounted
over and/or to the fusible link 614. The catheter 800 includes a lumen 626 extending
between a proximal opening at the proximal end 628 and a distal opening 630 at the
distal end 632. The catheter 800 further includes a cathode wire 616 and an anode
wire 618, each attached to the distal end of the catheter 800 and extending proximally
for coupling to a power supply (not shown) at the proximal end 628 of the catheter
800. In some embodiments, the wires 616, 618 are insulated from each other except
at the distal end of the catheter 602. An electrical discharge is produced between the
cathode and the anode wires 616, 618 at the distal end of the catheter 800. The
electrical discharge may be sufficient to disconnect the fusible link 614, breaking free
the implantable therapeutic device 500 from the remaining implantable therapeutic
devices 500. Such a configuration can be referred to as bipolar. Moreover, the skilled
artisan will appreciate that a monopolar configuration can also be employed, using a
ground pad on the patient's body and the fusible link comprises the anode.

In some embodiments, the catheters 600, 700, 800 deploy multiple
implantable therapeutic devices (e.g., microparticles) in batches. For example, a first
batch (i.e., plurality) of implantable therapeutic devices may be delivered
substantially simultaneously, and subsequently, a second batch (i.e., plurality) of
implantable therapeutic devices may be delivered substantially simultaneously. In
this context, it is understood that substantially simultaneously includes a single or
continuous activation of the deployment mechanism such as the pump 606, push shaft
612, or electrical activation of cathode wire 616 and anode wire 618, for delivering
the implantable therapeutic device, although not all of the implantable therapeutic
devices may exit from the catheters 600, 700, 800 at the exact same time. Any
number of batches useful to achieve the desired therapeutic effect may be deployed
via the catheters 600, 700, 800. Additionally, it is understood that the batches, e.g.,
the first and second batches of implantable therapeutic devices, may be sized
differently and/or include implantable therapeutic devices of different shapes, sizes
and/or configurations within each batch. In some embodiments, the first batch of implantable therapeutic devices may have a first dimension (e.g., diameter) whereas the second batch of implantable therapeutic devices may have a second dimension (e.g., diameter), which may be relatively larger than the first dimension. The dimensions of these batches of implantable therapeutic devices may be selected such that upon deployment in the body lumen surrounding the undesirable tissue, the implantable therapeutic devices block or occlude the body lumen, or are capable of delivering a predetermined amount of heat to the undesirable tissue.

FIGs. 9 and 10 illustrate methods of delivering implantable therapeutic devices to a tissue location. During operation, the catheters 600, 700, 800 may be advanced into a body lumen 750 or cavity through a natural opening or an incision in a body. The distal portion 602 is positioned adjacent to an undesirable tissue using, for example, an endoscope, for treatment. Once positioned, one or more implantable therapeutic devices (e.g., microparticles, which may alternatively be referred to as microseeds) (such as the microparticles 100, 500), having Curie temperatures ranging between 40°C and 440°C, are injected into the body lumen towards the undesirable tissue by applying pressurized fluid, mechanical push, or electrical discharge, as discussed above.

Any of the implantable therapeutic devices disclosed herein can be implanted via any suitable method or device. For example, the implantable therapeutic devices can be implanted by way of percutaneous orthoscopic, fluoroscopic, or MR (magnetic resonance) guided delivery; the implantable therapeutic devices can also be delivered surgically.

With regard to FIG. 11, in some embodiments, the elastic orifice 604 is configured to expand upon deployment of the implantable therapeutic device 100 and retract once the implantable therapeutic device has exited the elastic orifice 604. Further, in some embodiments, the elastic orifice 604 has sufficient elastic recoil to handle a variety of sizes of implantable therapeutic devices 100.

With regard to FIG. 12, in some embodiments, at least some of the first set of implantable therapeutic devices is injected into cavities in the vascular bed of the tissue 702 where the first set holds their position due to comparable sizes of the implantable therapeutic devices and the cavities (e.g., the implantable therapeutic devices are lodged in tissue or a body lumen). In some embodiments, such
implantable therapeutic devices block the supply of oxygen, which can assist in treating tissue 702. In some embodiments, the implantable therapeutic devices 100, 500 that are injected into the body lumen have different sizes, for example, a first set of implantable therapeutic devices having a first size and a second set of implantable therapeutic devices having a second size, which is larger or smaller than the first size. In some embodiments, the first set of implantable therapeutic devices may have a first Curie temperature and is configured for distal-most placement in the body lumen 750, adjacent to or in communication with the undesirable tissue. Further, the second set of implantable therapeutic devices may have a second Curie temperature and is configured for placement proximal to the first set, within the body lumen 750. In some embodiments, the first set has a first size of the microparticles ranging from 1 micron to 30 microns and the second set has a second size of microparticles ranging from 30 microns to 1000 microns. This is just an example. In some embodiments, the first set includes a first drug and the second set of microparticles includes a second drug different from the first drug.

In some embodiments, the implantable therapeutic devices are configured to release a drug into the tissue 702, as discussed above. In some embodiments, at least a portion of the implantable therapeutic devices are configured to degrade over time. In particular, the biodegradable polymer of some embodiments of the implantable therapeutic device 100 breaks down, with the biodegradable polymer being absorbed by surrounding tissue. Consequently, the magnetic nanoparticles, along with radiopaque particles, if present, can be consumed by macrophages within the body and removed via normal body function.

In some embodiments, the delivered implantable therapeutic devices are wirelessly heated through induction with radiofrequency (RF) signals that are high frequency alternating current (AC) signals. Referring to FIGs. 13A and 13B, an AC signal is pulsed to raise the temperature of the implantable therapeutic devices. The amount of energy delivered is based on frequency and pulse duration of the AC signal. For example, FIG. 13A illustrates an AC signal 802 having durations of active pulses and inactive pulses as 'a1' and 'b1', respectively, and an AC signal 804 having durations of active pulses and inactive pulses as 'a2' and 'b2', respectively. The ratio of durations of each active pulse and inactive pulse of the AC signal 802 is less than that of the AC signal 804, as shown in Equation 1. Stated differently, the on/off ratio
of time in FIG. 13A is less than the on/off ratio of time for that of FIG. 13B. Therefore, the energy delivered by the signal 804 is greater than the energy delivered by the signal 802.

\[ \frac{a_1}{b_1} < \frac{a_2}{b_2} \]  

The pulsed AC signals may be wirelessly applied to the injected implantable therapeutic devices, such as the implantable therapeutic devices 100, 500, so that the implantable therapeutic devices are subjected to an alternating field. The alternating field can be an electric field or, in some embodiments, a magnetic field can be applied. As a result of the applied field, Curie portions of the implantable therapeutic devices begin to rise in temperature. Consequently, when the injected implantable therapeutic devices contain a drug and/or radiopaque particles secured by a biocompatible thermoplastic polymer or ceramic layer, the rise in temperature of the Curie portions breaks open or otherwise melts the thermoplastic polymer or ceramic layer to release the drug and/or the radiopaque particles. It will be appreciated that, in some embodiments, release of the drug (e.g., drug 210) will not occur until the thermoplastic polymer or ceramic 208 has been sufficiently heated. In this way, it is possible to avoid releasing drugs into parts of the body where the drug is not desired, for example in the case of an errant implantable therapeutic device having a drug, by focusing the AC signal on only the desired region of treatment.

The exact distribution or density of the injected implantable therapeutic devices adjacent to or in the tissue 702 may be detected using a variety of techniques such as a CT scan, for example, based on the presence of the radiopaque particles. Such detection may be performed after the implantable therapeutic devices are injected into the body lumen but prior to heating the implantable therapeutic devices.

Based on the detected density of the implantable therapeutic devices and a priori knowledge about the amount of energy that may be transferred to each implantable therapeutic device by each active pulse of the AC signal, rise in temperature of each segment in the entire volume of the tissue 702 may be calculated. This calculated rise in temperature for each segment of the tissue 702 allows for a predetermined amount of energy to be delivered to the segments where the microparticle density is less, and vice versa, (as shown in FIG. 14), thereby achieving a homogeneous temperature rise over the entire volume of the tissue 702. Such
homogeneous temperature rise facilitates safe thermal treatment of the tissue 702. In order to provide a homogeneous temperature rise over the volume of tissue 702, having regions of higher/lower density of implantable therapeutic devices, some embodiments employ a distributed antenna array 900, as shown in FIG. 15. The distributed antenna array 900 can be used to direct greater amounts of energy to areas having a lower density of microparticles, for example, in order to achieve a uniform temperature rise over the area of treatment. In some embodiments and methods, however, the distributed antenna array 900 is used to provide an intentionally heterogeneous temperature rise. In this way, it is possible to increase the temperature more at desired locations.

In some embodiments, the distributed antenna array includes multiple spatially distributed antennas 902, 904, 906 (e.g., dipoles) as shown in FIG. 15. These antennas 902 are placed around the tissue 702 outside the body. Based on the microparticle density in the volume of the tissue 702, each antenna is tuned in pulse frequency of the AC signal for delivering a predetermined amount of power to the microparticles, thereby achieving the desired power distribution over the tissue 702. In some embodiments, for example, more power is applied to regions of cancerous tissue having a lower density of microparticles by providing such regions with more AC pulses.

Further, the inner magnetic kernel, such as the metallic shell 202 and the metallic core 302 discussed above, or magnetic nanoparticles 106 in the microparticles may be made of Curie materials with Curie temperatures higher than 45 ° C to raise the microparticle temperature beyond 45 ° C. In some embodiments, the surrounding thermoplastic polymer and/or ceramic layer moderate the release of energy over time and can act as thermal mass. Moreover, since each microparticle has a known loading of magnetic nanoparticles 106 or other Curie material, a temperature to which the microparticle is heated by a single active pulse of the AC signal can be determined. Consequently, a desired amount of energy can be transmitted to the tissue and homogeneous temperature can be maintained, as desired.

After each active pulse of the AC signal, the heat from the microparticles dissipates through the surrounding tissue and heats the volume of the tissue 702 to a desired temperature. Repeating such active pulses may raise the overall temperature of the tissue 702 to a further desired temperature level. Varying ON and OFF ratio between the pulses, allows the operator to precisely control the target temperature or
temperature profile across the tissue 702 for treatment, while staying just below the pain threshold of the patient. The amount of energy supplied per implantable therapeutic device, microparticle, nanoparticle, etc., can be regulated by pulse frequency or pulse duration, or both. Nonetheless, the upper temperature limit is determined by the Curie temperature.

In some embodiments, various medical devices such as balloons or stents may be coupled with Curie temperature-controlled elements such as implantable therapeutic devices 100 and 500 for treatment of various medical conditions. When subjected to an electromagnetic field, Curie portions of the implantable therapeutic devices begin to generate heat up until they reach the Curie temperature. The generated heat may be used to perform, without limitation, tissue modulation, tissue propagation, and nerve modulation for treatment. Tissue modulation may include, but is not limited to, (1) circulatory modulation involving heat treatment of blood vessel tissues and prostate tissues; (2) tumor modulation involving heat treatment of pre-cancerous and cancerous cells as well as lesions, undesirable tissue growth, and warts; (3) sensor modulation involving treatment of carotid body using heat; and (4) gland modulation involving heat treatment of mucocytes, for example, in salivary glands. Tissue propagation may involve heat treatment of endometriosis. Further, nerve modulation may involve heat treatment of both afferent and efferent sympathetic nerves as well as parasympathetic nerves. The implantable therapeutic devices, or portions thereof, may also be used for providing selectively paced or continuous heating to a target site within the body for mitigating pain such as chronic back pain and menstrual pain.

The following documents are incorporated herein by reference, each in its entirety:


Akin et al, "Nii-xCr\textsubscript{x} alloy for self controlled magnetic hyperthermia," Crystal Research and Technology, 2009, 44: 386-390


Haik et al. (U.S. Pat. No. 7,842,281, entitled "Magnetic particle composition for therapeutic hyperthermia").


Kim et al. (European Pat. Publ. No. EP 2 671 570 A2, entitled "Magnetic Nanoparticle, Having A Curie Temperature Which Is Within Biocompatible Temperature Range, And Method For Preparing Same").


Wang et al, "Reversible room-temperature magnetocaloric effect with large temperature span in antiperovskite compounds Gal-xCMn3+x (x=0, 0.06, 0.07, and 0.08)," J. Appl. Phys., 2009, 105, 083907-1 to 083907-5.
A description of some embodiments are contained in one or more of the following numbered statements:

Statement 1. A microparticle comprising:

an inner portion and an outer portion surrounding the inner portion, the inner portion comprising a biocompatible polymer and/or biocompatible ceramic and a plurality of magnetic nanoparticles, the magnetic nanoparticles having a Curie temperature between 40° and 100° C, the outer portion comprising a biocompatible polymer and/or biocompatible ceramic and a plurality of radiopaque nanoparticles.

Statement 2. The microparticle of statement 1, wherein the Curie temperature of the magnetic nanoparticles is greater than 45° C.

Statement 3. The microparticle of statement 2, wherein the Curie temperature of the magnetic nanoparticles is 42° to 48° C.

Statement 4. The microparticle of any one of the preceding statements, wherein the radiopaque nanoparticles comprise gold.

Statement 5. The microparticle of any one of the preceding statements having a diameter of 1-30 microns.

Statement 6. The microparticle of any one of the preceding statements, wherein the biocompatible polymer and/or biocompatible ceramic is biodegradable.

Statement 7. The microparticle of any one of the preceding statements, wherein the outer portion further comprises a drug.

Statement 8. A catheter comprising:

a catheter shaft defining a lumen and having a distal end portion, the distal end portion comprising an elastic orifice having a closed configuration and an open configuration;

a handle portion defining a reservoir, the reservoir in communication with the lumen, the reservoir having therein a liquid composition; and

a plurality of microparticles comprising a metallic component having a Curie temperature between 35° and 100° C, the microparticles configured to travel through the lumen, wherein the microparticles have a cross-section larger than the cross-section of the elastic orifice when the elastic orifice is in the closed configuration.

Statement 9. The catheter of statement 8, wherein the handle portion comprises a syringe, the syringe defining the reservoir.

Statement 10. The catheter of statement 9, wherein the reservoir has the microparticles therein.
Statement 11. The catheter of any one of statements 8, 9, and 10, wherein at least some of the microparticles contain a drug.

Statement 12. The catheter of any one of statements 8, 9, 10, and 11, wherein at least some of the microparticles include a polymeric portion.

Statement 13. The catheter of any one of statements 8-12, wherein at least some of the microparticles include a polymeric portion.

Statement 14. The catheter of any one of statements 8-12, wherein at least some of the microparticles have a metallic shell defining a cavity.

Statement 15. The catheter of statement 14, wherein the metallic shell comprises the metallic component.

Statement 16. The catheter of any one of statements 8-15, wherein the liquid composition is a solution or suspension of liquid and semi-liquid, the semi-liquid having a viscosity between 0.8 cP and 20,000 cP.

Statement 16. A catheter comprising:

- a catheter shaft defining a lumen and having a distal end portion, the distal end portion comprising an elastic orifice having a closed configuration and an open configuration;
- a handle portion defining a reservoir, the reservoir in communication with the lumen, the reservoir having therein a liquid composition; and
- a plurality of microparticles comprising a metallic component having a Curie temperature between 35° and 100° C, the microparticles configured to travel through the lumen, wherein the microparticles have a cross-section larger than the cross-section of the elastic orifice when the elastic orifice is in the closed configuration.

Statement 17. The catheter of statement 16, wherein the handle portion comprises a syringe, the syringe defining the reservoir.

Statement 18. The catheter of statement 16, wherein the reservoir has the microparticles therein.

Statement 19. The catheter of statement 16, wherein at least some of the microparticles contain a drug.

Statement 20. The catheter of statement 16, wherein at least some of the microparticles are radiopaque.

Statement 21. The catheter of statement 16, wherein at least some of the microparticles include a polymeric portion.

Statement 22. A microparticle comprising:
an inner portion and an outer portion surrounding the inner portion, the inner portion comprising a biocompatible polymer and/or biocompatible ceramic and a plurality of magnetic nanoparticles, the magnetic nanoparticles having a Curie temperature between 40° and 100° C, the outer portion comprising a biocompatible polymer and/or biocompatible ceramic and a plurality of radiopaque nanoparticles.

Statement 23. The microparticle of statement 22, wherein the Curie temperature of the magnetic nanoparticles is greater than 45° C.

Statement 24. The microparticle of statement 22, wherein the Curie temperature of the magnetic nanoparticles is 42° to 48° C.

Statement 25. The microparticle of statement 22 wherein the radiopaque nanoparticles comprise gold.

Statement 26. The microparticle of statement 22 having a diameter of 1-30 microns.

Statement 27. The microparticle of statement 22, wherein the biocompatible polymer and/or biocompatible ceramic is biodegradable.

Statement 28. The microparticle of statement 22, wherein the outer portion further comprises a drug.

Statement 29. The microparticle of statement 22, wherein the biocompatible polymer and/or biocompatible ceramic of the inner portion is a biocompatible polymer and consists of a polyamide.

Statement 30. The microparticle of statement 22, wherein the biocompatible polymer and/or biocompatible ceramic of the inner portion is a biocompatible polymer and consists of polylactic acid, poly(lactic-co-glycolic acid), or combinations thereof.

Statement 31. The microparticle of statement 22, wherein the biocompatible polymer and/or biocompatible ceramic of the inner portion is a biocompatible ceramic and consists of tri-calcium phosphate.

Statement 32. A method of treating a medical condition inside a body cavity or lumen comprising:

inserting a first plurality of microseeds into the body cavity or lumen, wherein the microseeds of the first plurality of microseeds have a diameter of 1-30 microns and a Curie temperature between 30° and 440° C; and

inserting a second plurality of microseeds into the body cavity or lumen subsequent to the first plurality of microseeds, wherein the microseeds of the second plurality of microseeds have a diameter of 30 microns to 1000 microns and a Curie temperature between 30° and 440° C;
the first plurality of microseeds being configured to perform a different function within the body cavity or lumen than the second plurality of microseeds.

Statement 33. The method of statement 32, wherein the function of the microseeds of the first plurality of microseeds is a first function, the first function is: releasing a drug therefrom, thermally treating tissue, cauterizing tissue, or occluding the body cavity or lumen and the function of the microseeds of the second plurality of microseeds is a second function, the second function is: releasing a drug therefrom, thermally treating tissue, cauterizing tissue, or occluding the body cavity or lumen, wherein the first function is different from the second function.

Statement 34. The method of statement 32, wherein the function of the microseeds of the first plurality of microseeds is a first function, the first function is raising the first plurality of microseeds to a first Curie temperature and the function of the microseeds of the second plurality of microseeds is a second function, the second function is raising the second plurality of microseeds to a second Curie temperature different from the first Curie temperature.

Statement 35. The method of statement 32, wherein the function of the microseeds of the first plurality of microseeds is a first function, the first function is releasing a first drug from the microseeds of the first plurality of microseeds and the function of the microseeds of the second plurality of microseeds is a second function, the second function is releasing a second drug from the microseeds of the second plurality of microseeds, wherein the first drug is different from the second drug.

The above disclosure is intended to be illustrative and not exhaustive. This description will suggest many variations and alternatives to one of ordinary skill in this field of art. All these alternatives and variations are intended to be included within the scope of the claims where the term "comprising" means "including, but not limited to." Those familiar with the art may recognize other equivalents to the specific embodiments described herein which equivalents are also intended to be encompassed by the claims.

Further, the particular features presented in the dependent claims can be combined with each other in other manners within the scope of the invention such that the invention should be recognized as also specifically directed to other embodiments having any other possible combination of the features of the dependent claims. For instance, for purposes of claim publication, any dependent claim which follows should be taken as alternatively written in a multiple dependent form from all prior
claims which possess all antecedents referenced in such dependent claim if such multiple dependent format is an accepted format within the jurisdiction (e.g. each claim depending directly from claim 1 should be alternatively taken as depending from all previous claims). In jurisdictions where multiple dependent claim formats are restricted, the following dependent claims should each be also taken as alternatively written in each singly dependent claim format which creates a dependency from a prior antecedent-possessing claim other than the specific claim listed in such dependent claim below.

This completes the description of the preferred and alternate embodiments of the invention. Those skilled in the art may recognize other equivalents to the specific embodiment described herein which equivalents are intended to be encompassed by the claims attached hereto.
What is claimed is:

1. A microparticle comprising:
   a plurality of magnetic nanoparticles, the magnetic nanoparticles having a Curie temperature between 40° and 100° C;
   a plurality of radiopaque nanoparticles; and
   a biocompatible polymer and/or biocompatible ceramic.

2. The microparticle of claim 1, wherein the Curie temperature of the magnetic nanoparticles is greater than 45° C.

3. The microparticle of claim 1, wherein the Curie temperature of the magnetic nanoparticles is in the range of 42° to 48° C.

4. The microparticle of any one of claims 1-3, wherein the radiopaque nanoparticles comprise gold.

5. The microparticle of any one of claims 1-4, wherein the microparticle has a diameter in the range of 1-30 microns.

6. The microparticle of any one of claims 1-5, wherein the biocompatible polymer and/or biocompatible ceramic is biodegradable.

7. The microparticle of any one of claims 1-6, wherein the biocompatible polymer and/or biocompatible ceramic further comprises a therapeutic drug.

8. The microparticle of any one of claims 1-7, wherein the biocompatible polymer and/or biocompatible ceramic is a biocompatible polymer having a melting point less than the Curie temperature of the magnetic nanoparticles.

9. The microparticle of any one of claims 1-8, wherein the biocompatible polymer and/or biocompatible ceramic is a biocompatible polymer comprising a polyamide.
10. The microparticle of any one of claims 1-8, wherein the biocompatible polymer and/or biocompatible ceramic is a biocompatible polymer comprising polylactic acid, poly(lactic-co-glycolic acid), or combinations thereof.

11. The microparticle of any one of claims 1-8, wherein the biocompatible polymer and/or biocompatible ceramic is a biocompatible ceramic comprising tricalcium phosphate.

12. A catheter comprising:
   a catheter shaft defining a lumen and having a distal end portion, the distal end portion comprising an elastic orifice having a closed configuration and an open configuration;
   a handle portion defining a reservoir, the reservoir in communication with the lumen, the reservoir having therein a liquid composition; and
   a plurality of microparticles comprising a metallic component having a Curie temperature between 35° and 100° C, the microparticles configured to travel through the lumen, wherein the microparticles have a cross-section larger than the cross-section of the elastic orifice when the elastic orifice is in the closed configuration.

13. The catheter of claim 12, wherein the handle portion comprises a syringe, the syringe defining the reservoir.

14. The catheter of claim 13, wherein the microparticles are disposed within the reservoir.

15. The catheter of any one of claims 12-14, wherein at least some of the microparticles contain a therapeutic drug.
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<th>Relevant to claim No.</th>
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<td>X</td>
<td>DE 10 2010 022926 A1 (SIEMENS AG [DE]) 8 December 2011 (2011-12-08) paragraphs [0023], [0024], [0026], [0028], [0045]; claims 1,5</td>
<td>1-11</td>
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<td>A</td>
<td>US 2014/056982 A1 (ANDERSON RUSSELL J [US]) 27 February 2014 (2014-02-27) paragraphs [0016], [0018], [0041], [0042]; claims 5,6, 10</td>
<td>5,9-11</td>
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See patent family annex.

* Special categories of cited documents:
  - "A" document defining the general state of the art which is not considered to be of particular relevance
  - "E" earlier application or patent but published on or after the international filing data
  - "L" document which may throw doubts on priority claim(s) one(s) which is cited to establish the publication date of another citation or other special reason (as specified)
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**"T"** later document published after the international filing data or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

**"X"** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

**"Y"** document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

**"A"** document member of the same patent family
This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. □ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. □ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. □ Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. □ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. □ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. □ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. □ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

   1-11

Remark on Protest

□ The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.

□ The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.

□ No protest accompanied the payment of additional search fees.
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-11

   A microparticule comprising magnetic nanoparticles, radiopaque nanoparticles, and a polymer

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2. Claims: 12-15

   A catheter with an orifice configured to disperse microparticules

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