

BIOCOMPATIBLE POLYMERS FOR USE IN ONCOLOGICAL IMAGING AND RADIATION

Related Application

[01] This application claims convention priority from Australian Provisional Patent Application No. 2023903450, filed 27 October 2023. The content of AU'450 is incorporated herein in its entirety.

Field of the Invention

[02] The present invention relates to biologically-compatible polymers and the present inventors' surprising discovery that such polymers may be used as a physical "spacer" and/or "hydrodissection solution" in oncological imaging and radiation.

[03] The present invention further relates to the discovery that at concentrations above about 100 mg/mL, Applicant's proprietary polymers PNPFO and PPHO can be used to generate space between different organs by forming a hydrogel at the point of administration. Such an observation has three principal applications: 1) to generate space to reduce the effect of therapeutic radiation on the surrounding tissues; 2) to fill a gap to reduce/normalise air pockets and therefore enhance the accuracy of dose calculation; and 3) to protect tissues, *e.g.*, rectal tissue against direct radiation exposure.

[04] The present invention further relates to the discovery that at concentrations between about 25 mg/mL and about 100 mg/mL, Applicant's proprietary polymers PNPFO and PPHO can be used for hydrodissection of different tissues as a non-irritant and visible solution under ultrasound and/or CT-scan. Such an observation has two principal applications: 1) to be injected into a tissue to dissect the target tissue/s; and (2) to be visible under ultrasound and/or CT-scan for a more accurate needle placement/hydrodissection.

[05] Accordingly, the present invention is envisaged to find utility in medicine, more particularly, in oncology and related fields.

[06] Although the present invention will be described hereinafter with reference to its preferred embodiment, it will be appreciated by those of skill in the art that the spirit and scope of the invention may be embodied in many other forms.

Background of the Invention

[07] Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common

general knowledge in the field.

[08] Despite recent advances in focussing the beam, the use of radiation therapy to treat cancer inevitably involves exposure of unaffected tissues. As a result, patients may experience symptoms associated with damage to normal tissue during the course of therapy for a few weeks after therapy or months or years later. Symptoms may be due to cell death or wound healing initiated within irradiated tissue, and may be precipitated by exposure to further injury or trauma. Many factors contribute to the risk and severity of normal tissue reactions. Such factors are site-specific and vary with time after treatment.

[09] Radiation treatment of cancer is based on the fact that rapidly dividing cells are more sensitive to radiation. Cancer is made up of rapidly dividing cells, so the cancer cells are expected to be more sensitive to radiation than normal tissue. The major challenge in radiation therapy is to eradicate the cancer without unduly damaging surrounding normal tissues. Even today, the amount of radiation delivered to the tumour is limited by the collateral damage to nearby normal tissues.

[010] Treatments that reduce the risk or severity of damage to normal tissue or that facilitate the healing of radiation injury are being developed. These could greatly improve the quality of life of patients treated for cancer. The severity and frequency of normal tissue side effects can be reduced by modern, more precise therapies, such as particle therapy which can be used to reduce the radiation dose to normal tissue reducing side effects, or dose escalation improving tumour control.

[011] The prostate is both an accessory gland of the male reproductive system and a muscle-driven mechanical switch between urination and ejaculation. Anatomically, the prostate is found below the bladder, with the urethra passing through it. It also is in close proximity to the rectum, penis, testicles, seminal vesicle and lymph nodes.

[012] Prostate cancer is one of the most common cancers affecting older men across the Western world. Where a decision is made to treat the cancer, the two main options are prostatectomy (*i.e.*, removal) or radiation therapy. The radiation can be delivered in several ways, including brachytherapy (using seeds that are implanted in the patient's body) and external beam radiation that projects the energy through the skin.

[013] Given the location of the prostate, as identified above, the potential side effects of external beam radiation therapy for prostate cancer may be extensive and may include frequent urination, difficult or painful urination, blood in the urine, urinary leakage, abdominal cramping, diarrhea, painful bowel movements, rectal bleeding, rectal leaking, fatigue, sexual dysfunction including diminished erectile function or decrease in the

volume of semen, skin reactions (similar to sunburn), and secondary cancers in the region of the radiation.

[014] In extreme cases, the likelihood of significant damage to proximal cells or organs may preclude the use of radiation therapy in the treatment of prostate cancer. Accordingly, any means of decreasing a patient's risk profile must remain a goal of radiation oncologists and therapists (can be referred to as radiographers) alike.

[015] Hydrodissection is the use of a directed jet of water to surgically separate tissues. It is generally used to develop tissue planes or divide soft tissues with less trauma than dissection using a cutting instrument. By using an appropriate pressure, tissue separation will tend to follow the path of least resistance that is close to the direction of the jet. For instance, in the placement of hydrogel spacer, hydrodissection is used to generate a space in perirectal fat prior to the application of the hydrogel. Alternatively, in cataract surgery hydrodissection is used to release the lens from its capsule by projecting a continuous flow of water from a cannula under the flap of the anterior capsule, which lifts the capsule membrane from the lens. By directing the flow, the surgeon lifts the membrane around the sides and back of the capsule until the lens is completely loose. Hydrodissection is also used in general surgery to release a trapped nerve or to reduce intraoperative blood losses, etc.

[016] In a different sector of the biomedical field, the present Applicant, Trimph IP Pty Ltd, of Sydney, Australia, has been active over the past decade in patenting a suite of biocompatible polymers for medical applications. All of the patents and patent publications referred to herein are incorporated by reference in their respective entireties.

[017] WO 2013/091001 (PCT/AU2012/001566) relates to polymers, especially polymers useful as hydrogels, and to the use of hydrogels for repair or restoration of tissue. In particular, the polymers and hydrogels of WO'001 can be used for the repair or restoration of cartilage, especially articular cartilage. The polymers comprise at least a monomer for binding water, a monomer for imparting mechanical properties and a monomer for binding to an extracellular protein. The hydrogels comprise a polymer comprising at least a monomer for binding water and a monomer for binding to an extracellular protein. Crosslinking polymers by binding of the extra-cellular matrix protein forms hydrogels.

[018] A preferred polymer disclosed in WO'001 is Poly(NIPAAm-*co*-NAS-*co*-(PLA/HEMA)-*co*-OEGMA), *i.e.*, "PNPHO". The polymer PNPHO preferably comprises OEGMA in an amount of from about 1 and about 15 mol%, PLA/HEMA in an amount of from about 5 and about 50 mol%, NAS in an amount of up to 15 mol%, and NIPAAm in

an amount which makes up the remainder to 100% of the polymer composition, for example, from about 50 to about 85 mol%. For certainty, the percentages recited relate to the composition of the final polymer and not the feed amounts utilised when forming the polymer.

[019] A preferred form of the polymer PNPHO is a polymer of Formula (I), as drawn below. In addition, x is in the range of 1-1000 and y is in the range of 1-1000 and m, n, p, and q are in the range of 1-20. A person skilled in the art will be aware that the monomers A, B, C and D may be present in the polymer in any order, provided that the required water-binding, strengthening and/or cross-linking capabilities are achieved.

[020] WO 2017/035587 (PCT/AU2016/050817) discloses biocompatible materials useful for tissue regeneration and repair, wherein the bioactive polymer may be in the form of a hydrogel, for example a thermoresponsive hydrogel. The bioactive polymer and resulting hydrogel of WO'587 may be used for the regeneration of bone tissue. Accordingly, the reference teaches methods of treating a bone defect in a mammal, the methods comprising administering a therapeutically effective amount of a hydrogel formed by the bioactive polymer to the mammal to treat the bone defect.

[021] WO 2017/015703 (PCT/AU2016/050653) discloses a polymer comprising at least one antiseptic/analgesic/anti-inflammatory monomeric unit in conjunction with at least three further monomeric units, the three further monomeric units eliciting properties selected from the group consisting of: temperature activation, water solubility, mechanical strength, protein/polysaccharide bonding capacity, and combinations thereof. In particular, WO'703 discloses a polymer, wherein the water-soluble monomeric unit is a hydrophilic ethylene glycol (OEGMA) moiety; the mechanical strength-conferring monomeric unit is polylactide-co-2-hydroxy-ethylmethyl acrylate (PLA/HEMA); the protein-reactive monomeric unit is an N-acryloxysuccinimide (NAS) moiety; and the thermosetting monomeric unit is an N- isopropyl acrylamide (NIPAAm) moiety. The antiseptic/analgesic/anti-inflammatory monomeric unit comprises a methacrylic ester derivative of salicylic acid (5-HMA or 4-HMA, or a combination thereof).

[022] WO 2021/119727 (PCT/AU2020/051332) teaches a composition comprising a polymer and a natural or synthetic peptide or protein (NSPP) as Thymosin beta-4. The polymer comprises a first monomer for binding water, a second monomer for imparting mechanical properties, a third monomer for binding to an NSPP and a fourth monomer for imparting phase-transition behaviour. In particular, the composition forms an adhesive and flowable hydrogel upon administration into the body or onto the body surface, thereby

assists in tissue repair and regeneration. Accordingly, WO'727 discloses methods of tissue repair and/or regeneration, the methods comprising administering the compositions by injection or by administering an aerosol, thereby to form a hydrogel at the body temperature of a mammal.

[023] Finally, WO 2023/201397 (PCT/AU2023/050329) discloses a new polymer, "PPHO", *i.e.*, Poly(N-isopropylacrylamide-*co*-(polylactide/2-hydroxy methacrylate)-*co*-(oligo (ethylene glycol) / Poly(NIPAAm-*co*-(PLA/HEMA)-*co*-OEGMA)).

[024] The polymer PPHO preferably comprises OEGMA in an amount of from about 1 and about 15 mol%, PLA/HEMA in an amount of from about 5 and about 50 mol%, and NIPAAm in an amount which makes up the remainder to 100% of the polymer composition, for example, from about 50 to about 85 mol%. In preferred embodiments, PPHO comprises OEGMA in about 1 to 15 mol% and/or PLA/HEMA in about 15 to 50 mol% and/or NIPAAm in an amount of about 50 to 85 mol%. As above, the percentages recited herein relate to the composition of the final polymer and not the feed amounts utilised when forming the polymer.

[025] It is an object of the present invention to overcome or ameliorate at least one of the disadvantages of the prior art, or to provide a useful alternative.

[026] There is a general need in the art for new means of lessening damage to surrounding cells/tissues as a result of radiation therapy used in the treatment of ailments such as prostate cancer.

[027] There is a general need in the art for new means of reducing damage to tissues separated during hydrodissection procedures.

[028] It is against this background that the present invention has been developed. Various embodiments of the present invention may find utility relating to one or more of the general needs identified above.

[029] In particular, the present invention is found to be useful in establishing a safe, non-irritant, CT-scan-visualisable and injectable physical spacer between an organ being irradiated (*e.g.*, prostate) and surrounding cells/tissues/organs (*e.g.*, rectum).

[030] Moreover, the present invention is found to be useful in establishing a safe, non-irritant, ultrasound visualisable and injectable solution for hydrodissection of different tissues (*e.g.*, perirectal fat).

[031] Although the invention will be described with reference to specific examples it will be appreciated by those skilled in the art that the invention may be embodied in many other forms.

Summary of the Invention

[032] In a broad form, the present invention relates to administering a polymer to a treatment site at or proximal with a target tissue (*e.g.*, the human prostate), the polymer thereby forming a hydrogel at body temperature. Such hydrogel can have different applications for radiation oncology and broader medical purposes, including: 1) to be applied as a non-irritant solution, visible with ultrasound for accurate hydrodissection (*e.g.*, for perirectal fat). Such hydrodissection is facilitated by accurate injection of a solution of the inventive polymer/s to prevent side effects such as rectal wall infiltration in the application of spacers; 2) to provide physical spacing between the tissue and nearby cells/tissues/organs (*e.g.*, the human rectum). Such physical spacing/isolation of the prostate from the rectum allows radiation therapy to focus on the isolated target tissue without substantially affecting the cells/tissues/organs spaced from it by the polymer hydrogel; and 3) to use as a space filler to reduce the presence of air pocket/air cavity in target radiation therapy (*e.g.*, after lumpectomy and MammoSite treatment). The inventive hydrogel filler to remove air pockets/cavities can reduce the heterogeneity of the air pockets/cavities in targeted radiation therapy (*e.g.*, MammoSite) and may thereby reduce dosage errors to the tissue located near the air/tissue interface due to lack of attenuation and inverse square correction.

[033] According to a first aspect of the present invention there is provided a polymer for administering at a treatment site to form a hydrogel to physically space/isolate target tissue for radiotherapy and/or to hydrodissect a tissue/organ and/or to physically space/isolate target tissue for radiotherapy and/or to fill a site to reduce air pockets, the polymer comprising:

[034] a first monomer for binding water;

[035] a second monomer for imparting mechanical properties;

[036] optionally, a third monomer for binding to a natural or synthetic peptide or protein (NSPP); and

[037] a fourth monomer for imparting phase-transition behaviour.

[038] According to a second aspect of the present invention there is provided a polymer for administering at a treatment site to form a hydrogel to physically hydrodissect two or more abutting tissues, the polymer comprising:

[039] a first monomer for binding water;

[040] a second monomer for imparting mechanical properties;

[041] optionally, a third monomer for binding to a natural or synthetic peptide or protein (NSPP); and

[042] a fourth monomer for imparting phase-transition behaviour.

[043] The preferred embodiments outlined below are applicable to both first and second aspects of the invention, unless specified otherwise.

[044] In an embodiment, the polymer is Poly(NIPAAm-*co*-NAS-*co*-(PLA/HEMA)-*co*-OEGMA), *i.e.*, “PNPHO”. The polymer PNPHO preferably comprises OEGMA in an amount of from about 1 and about 15 mol%, PLA/HEMA in an amount of from about 5 and about 50 mol%, NAS in an amount of up to 15 mol%, and NIPAAm in an amount which makes up the remainder to 100% of the polymer composition, for example, from about 50 to about 85 mol%.

[045] In an embodiment, the polymer is Poly(N-isopropylacrylamide-*co*-(polylactide/2-hydroxy methacrylate)-*co*-(oligo (ethylene glycol) / Poly(NIPAAm-*co*-(PLA/HEMA)-*co*-OEGMA) *i.e.*, “PPHO”. The polymer PPHO preferably comprises OEGMA in an amount of from about 1 and about 15 mol%, PLA/HEMA in an amount of from about 5 and about 50 mol%, and NIPAAm in an amount which makes up the remainder to 100% of the polymer composition, for example, from about 50 to about 85 mol%.

[046] In an embodiment, the first monomer is selected from: polyethers, polyvinyl alcohol (PVA); poly(vinyl pyrrolidone) (PVP); poly(amino acids) and dextran.

[047] In an embodiment, the polyethers are selected from: polyethylene glycol (PEG), oligo(ethylene glycol) (OEG), polyethylene oxide (PEO), polyethylene oxide-*co*-propylene oxide (PPO), *co*-polyethylene oxide block or random copolymers thereof.

[048] In an embodiment, the first monomer is oligo (ethylene) glycol monomethyl ether methacrylate (OEGMA).

[049] In an embodiment, the second monomer is a methacrylate, or a random *co*-polymer comprising a methacrylate.

[050] In an embodiment, the second monomer is selected from: hydroxyethyl methacrylate (HEMA), a hydroxyethyl methacrylate poly(lactic acid) copolymer (PLA/HEMA), poly(lactic acid), poly(caprolactone), poly(glycolide), poly(glycolide-*co*-lactide) or poly(glycolide-*co*-caprolactone).

[051] In an embodiment, the second monomer is hydroxyethyl methacrylate poly(lactic acid) (PLA/HEMA).

[052] In an embodiment, the third monomer has electrophilic functional groups for binding to the NSPP.

[053] In an embodiment, the third monomer is selected from: N-hydroxysulfosuccinimide (SNHS), N-hydroxyethoxylated succinimide (ENHS), and N-acryloxysuccinimide (NAS).

[054] In an embodiment, the third monomer is N-acryloxysuccinimide (NAS).

[055] In an embodiment, the fourth monomer has a lower critical solution temperature (LCST) less than about 37 °C.

[056] In an embodiment, the fourth monomer is selected from: poly(ethylene oxide)/poly(propylene oxide) and poly(N-isopropylacrylamide) (PNIPAAm) homopolymers and copolymers.

[057] In an embodiment, the fourth monomer is (N-isopropylacrylamide) (NIPAAm).

[058] In an embodiment, the polymer comprises the first monomer in an amount of from about 1 to about 15 mol%.

[059] In an embodiment, the polymer comprises the second monomer in an amount of from about 5 to about 50 mol%.

[060] In an embodiment, the polymer comprises the third monomer in an amount of from about 0 to about 15 mol%.

[061] In an embodiment, the polymer comprises the fourth monomer in an amount of from about 50 to about 85 mol%.

[062] In an embodiment, the polymer comprises: the first monomer in an amount of from about 1 to about 15 mol%; the second monomer in an amount of from about 5 to about 50 mol%; the third monomer in an amount of 0 to about 15 mol%; and the fourth monomer in an amount which makes up the remainder to 100% of the polymer.

[063] In an embodiment, the first monomer is OEGMA; the second monomer is PLA/HEMA; the third monomer is NAS; and the fourth monomer is NIPAAm,

[064] wherein the polymer comprises: OEGMA in an amount of from about 1 to about 15 mol%; PLA/HEMA in an amount of from 5 to about 50 mol%; NAS in an amount of from 0 to about 15 mol%; and NIPAAm in an amount of up to about 85 mol%.

[065] In an embodiment, to administer the polymer at the treatment site, it is dissolved or dispersed in aqueous solution at a polymer concentration greater than about 100 mg/mL.

[066] In respect of the first aspect, the polymer concentration is greater than about 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490 or 500 mg/mL.

[067] In respect of the first aspect, in one embodiment, to administer the polymer at the treatment site, it is dissolved or dispersed in aqueous solution at a polymer concentration

greater than about 280 mg/mL.

[068] In an embodiment of the first aspect, the target tissue for radiotherapy is a human prostate gland. In other embodiments, the target tissue for radiotherapy is a human head and neck, chest and breast, abdomen and gastrointestinal organs, pelvis, genitourinary and colorectal organs, limbs or skin.

[069] In an embodiment of the first aspect, administering the polymer at the treatment site is performed by injection. Alternatively, the polymer may be administered dermally or by implantation.

[070] In an embodiment of the first aspect, the polymer is injected between a patient's rectum and prostate to provide a temporary space between said organs, thereby reducing the dosage of radiation delivered to the rectum where the prostate is the target tissue.

[071] In respect of the second aspect of the invention, to administer the polymer at the treatment site, it is dissolved or dispersed in aqueous solution at a polymer concentration between about 25 mg/mL and about 100 mg/mL.

[072] In an embodiment of the second aspect, the concentration of the polymer in aqueous solution is about 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or about 100 mg/mL.

[073] In an embodiment of the second aspect, administering the polymer at the treatment site is performed by injection.

[074] In an embodiment, the first monomer is OEGMA; the second monomer is PLA/HEMA; the third monomer is NAS; and the fourth monomer is NIPAAm.

[075] In an embodiment, the polymer comprises: OEGMA in an amount of from about 1 to about 15 mol%; PLA/HEMA in an amount of from 5 to about 50 mol%; NAS in an amount of from 0 to about 15 mol%; and NIPAAm in an amount of up to about 85 mol%;

[076] In an embodiment, the target tissue for radiotherapy is a human prostate gland; and

[077] In an embodiment, the polymer is present in a concentration of about 280 mg/mL.

[078] According to a third aspect of the present invention there is provided a method for physically spacing/isolating a target tissue for radiotherapy, the method comprising administering to a subject in need thereof an effective concentration of a polymer as defined according to the first aspect of the present invention at or proximal to the target tissue.

[079] According to a fourth aspect of the present invention there is provided a method for physically hydrodissecting two or more abutting tissues at a treatment site, the method comprising administering to a subject in need thereof an effective concentration of a

polymer as defined according to the second aspect of the present invention at or proximal to the treatment site.

[080] The preferred embodiments outlined below are applicable to both third and fourth aspects of the invention, unless specified otherwise.

[081] In an embodiment, the polymer comprises: a first monomer for binding water; a second monomer for imparting mechanical properties; optionally, a third monomer for binding to a natural or synthetic peptide or protein (NSPP); and a fourth monomer for imparting phase-transition behaviour.

[082] In an embodiment, the polymer comprises: OEGMA in an amount of from about 1 to about 15 mol%; PLA/HEMA in an amount of from 5 to about 50 mol%; NAS in an amount of from 0 to about 15 mol%; and NIPAAm in an amount of up to about 85 mol%.

[083] In an embodiment, the administration is performed at or about body temperature.

[084] In an embodiment, the administration is performed by injection. Alternatively, the polymer may be administered dermally or by implantation.

[085] In an embodiment, the target tissue for radiotherapy is a human prostate gland. In other embodiments, the target tissue for radiotherapy is a human head and neck, chest and breast, abdomen and gastrointestinal organs, pelvis, genitourinary and colorectal organs, limbs or skin.

[086] In an embodiment of the third aspect, to administer the polymer at the treatment site, it is dissolved or dispersed in aqueous solution at a polymer concentration of greater than about 100 mg/mL.

[087] In respect of the third aspect, the polymer concentration is greater than about 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490 or 500 mg/mL.

[088] In an embodiment of the third aspect, to administer the polymer at the treatment site, it is dissolved or dispersed in aqueous solution at a polymer concentration of about 280 mg/mL.

[089] In respect of the third aspect, the polymer concentration is greater than about 280, 285, 290, 295, 300, 305, 310, 315, 320, 325, 330, 335, 340, 345, 350, 355, 360, 365, 370, 375, 380, 385, 390, 395, 400, 405, 410, 415, 420, 425, 430, 435, 440, 445, 450, 455, 460, 465, 470, 475, 480, 485, 490, 495 or 500 mg/mL.

[090] In respect of the third aspect, the polymer is injected between a patient's rectum and prostate to provide a temporary space between said organs, thereby reducing the

dosage of radiation delivered to the rectum where the prostate is the target tissue.

[091] In respect of the fourth aspect of the invention, to administer the polymer at the treatment site, it is dissolved or dispersed in aqueous solution at a polymer concentration between about 25 mg/mL and about 100 mg/mL.

[092] In an embodiment of the fourth aspect, the concentration of the polymer in aqueous solution is about 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or about 100 mg/mL.

[093] In an embodiment of the fourth aspect, administering the polymer at the treatment site is performed by injection.

[094] According to a fifth aspect of the present invention there is provided use of a polymer as defined according to the first aspect of the present invention in the manufacture of a medicament for physically spacing/isolating a target tissue for radiotherapy.

[095] According to a sixth aspect of the present invention there is provided use of a polymer as defined according to the second aspect of the present invention in the manufacture of a medicament for physically hydrodissecting two or more abutting tissues at a treatment site.

[096] The preferred embodiments outlined below are applicable to both fifth and sixth aspects of the invention, unless specified otherwise.

[097] In an embodiment, the polymer comprises: a first monomer for binding water; a second monomer for imparting mechanical properties; optionally, a third monomer for binding to a natural or synthetic peptide or protein (NSPP); and a fourth monomer for imparting phase-transition behaviour.

[098] In an embodiment, the polymer comprises: OEGMA in an amount of from about 1 to about 15 mol%; PLA/HEMA in an amount of from 5 to about 50 mol%; NAS in an amount of from 0 to about 15 mol%; and NIPAAm in an amount of up to about 85 mol%.

[099] In an embodiment, the administration is performed at or about body temperature.

[0100] In an embodiment, the administration is performed by injection. Alternatively, the polymer may be administered dermally or by implantation.

[0101] In an embodiment, the target tissue for radiotherapy is a human prostate gland. In other embodiments, the target tissue for radiotherapy is a human head and neck, chest and breast, abdomen and gastrointestinal organs, pelvis, genitourinary and colorectal organs, limbs or skin

[0102] In an embodiment of the fifth aspect, to administer the polymer at the treatment site, it is dissolved or dispersed in aqueous solution at a polymer concentration of greater

than about 100 mg/mL.

[0103] In respect of the fifth aspect, the polymer concentration is greater than about 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490 or 500 mg/mL.

[0104] In an embodiment of the fifth aspect, to administer the polymer at the treatment site, it is dissolved or dispersed in aqueous solution at a polymer concentration of about 280 mg/mL.

[0105] In respect of the fourth aspect of the invention, the polymer concentration is preferably greater than about 280, 285, 290, 295, 300, 305, 310, 315, 320, 325, 330, 335, 340, 345, 350, 355, 360, 365, 370, 375, 380, 385, 390, 395, 400, 405, 410, 415, 420, 425, 430, 435, 440, 445, 450, 455, 460, 465, 470, 475, 480, 485, 490, 495 or 500 mg/mL.

[0106] In an embodiment of the fifth aspect, the polymer is injected between a patient's rectum and prostate to provide a temporary space between said organs, thereby reducing the dosage of radiation delivered to the rectum where the prostate is the target tissue.

[0107] According to a seventh aspect of the present invention there is provided a kit for physically spacing/isolating target tissue for radiotherapy, the kit comprising a polymer as defined according to the first aspect of the present invention; means for administering said polymer; and instructions for administering said polymer at or proximal to said target tissue.

[0108] In an embodiment, the polymer comprises: a first monomer for binding water; a second monomer for imparting mechanical properties; optionally, a third monomer for binding to a natural or synthetic peptide or protein (NSPP); and a fourth monomer for imparting phase-transition behaviour.

[0109] In an embodiment, the polymer comprises: OEGMA in an amount of from about 1 to about 15 mol%; PLA/HEMA in an amount of from 5 to about 50 mol%; NAS in an amount of from 0 to about 15 mol%; and NIPAAm in an amount of up to about 85 mol%.

[0110] In an embodiment, the administration is performed at or about body temperature.

[0111] In an embodiment, the administration is performed by injection. Alternatively, the polymer may be administered dermally or by implantation.

[0112] In an embodiment, the target tissue for radiotherapy is a human prostate gland. In other embodiments, the target tissue for radiotherapy is a human head and neck, chest and breast, abdomen and gastrointestinal organs, pelvis, genitourinary and colorectal organs, limbs or skin.

[0113] In an embodiment, to administer the polymer at the treatment site, it is dissolved or dispersed in aqueous solution at a polymer concentration of about 280 mg/mL.

[0114] Preferably, the polymer concentration is greater than about 280, 285, 290, 295, 300, 305, 310, 315, 320, 325, 330, 335, 340, 345, 350, 355, 360, 365, 370, 375, 380, 385, 390, 395, 400, 405, 410, 415, 420, 425, 430, 435, 440, 445, 450, 455, 460, 465, 470, 475, 480, 485, 490, 495 or 500 mg/mL.

[0115] In an embodiment, the polymer is injected between a patient's rectum and prostate to provide a temporary space between said organs, thereby reducing the dosage of radiation delivered to the rectum where the prostate is the target tissue.

[0116] In another embodiment, to administer the polymer at the treatment site, it is dissolved or dispersed in aqueous solution at a polymer concentration of between about 25 mg/mL and about 100 mg/mL.

[0117] In an embodiment, the concentration of the polymer in aqueous solution is about 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or about 100 mg/mL.

Definitions and Nomenclature

[0118] In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments of the invention only and is not intended to be limiting. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one having ordinary skill in the art to which the invention pertains.

[0119] Unless the context clearly requires otherwise, throughout the description and the claims, the words "comprise", "comprising", and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

[0120] The terms "preferred" and "preferably" refer to embodiments of the invention that may afford certain benefits, under certain circumstances. However, other embodiments may also be preferred, under the same or other circumstances. Furthermore, the recitation of one or more preferred embodiments does not imply that other embodiments are not useful and is not intended to exclude other embodiments from the scope of the invention.

[0121] As used herein a wording defining the limits of a range or length such as, for example, "from 1 to 5" means any integer from 1 to 5, *i.e.*, 1, 2, 3, 4 and 5. In other words, any range defined by two integers explicitly mentioned is meant to comprise and disclose

any integer defining the limits and any integer comprised in the range.

[0122] Other than in the operating examples, or where otherwise indicated, all numbers expressing quantities of ingredients or reaction conditions used herein are to be understood as modified in all instances by the term “about”. The examples are not intended to limit the scope of the invention. In what follows, or where otherwise indicated, “%” will mean “weight %”, “ratio” will mean “weight ratio” and “parts” will mean “weight parts”.

[0123] Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard variations found in their respective testing measurements.

[0124] The present specification uses the following abbreviations:

HEMA	Hydroxyethyl methacrylate
LA	Lactic acid
NAS	N-acryloxysuccinimide
NIPAAm	N-isopropylacrylamide
NSPP	Natural or synthetic peptide or protein
OEG	Oligo(ethylene glycol)
OEGMA	Oligo(ethylene) glycol monomethyl ether methacrylate
PBS	Phosphate-buffered saline
PEG	Polyethylene glycol
PEO	Polyethylene oxide
PLA	Poly(lactic acid)
PLA/HEMA	Hydroxyethyl methacrylate poly(lactic acid)
PPO	Polyethylene oxide- <i>co</i> -propylene oxide
PVA	Polyvinyl alcohol
PVP	Poly(vinyl pyrrolidone)
PNPHO	Poly(N-isopropylacrylamide- <i>co</i> -(N-acryloxysuccinimide)- <i>co</i> -(polylactide/2-hydroxy methacrylate)- <i>co</i> -(oligo (ethylene glycol) / Poly(NIPAAm- <i>co</i> -NAS- <i>co</i> -(PLA/HEMA)- <i>co</i> -OEGMA), <i>e.g.</i> , Formula (I)
PPHO	Poly(N-isopropylacrylamide- <i>co</i> -(polylactide/2-hydroxy methacrylate)- <i>co</i> -(oligo (ethylene glycol) / Poly(NIPAAm- <i>co</i> -(PLA/HEMA)- <i>co</i> -OEGMA), <i>e.g.</i> , Formula (II)

Brief Description of the Drawings

[0125] Preferred embodiments of the invention will now be described, by way of example only, with reference to the accompanying drawings in which:

[0126] The injected solution of aqueous PNPHO and/or PPHO forms a hydrogel at the body temperature. A simulated test shown in *Figure 1* confirmed that the polymer hydrogel has a CT-Hounsfield Unit of between 10 and 60 (HU) which is similar to water and soft tissue equivalent and therefore suitable to guarantee precise radiation oncology by obtaining the relationship between HU and electron densities of the structures exposed to radiation beams. *Figure 1* shows the setup to acquire the CT-Hounsfield Unit of polymer hydrogel (simulated at 37 °C). The simulation was completed with 280 mg/mL of PNPHO hydrogel and daily Quality Assurance (QA) LAP Wike Phantom. The visualised polymer hydrogel is shown by the yellow arrows.

[0127] *Figure 2* demonstrates that the injection of the polymer/s forms a hydrogel at body temperature, which in turn provide structure/space for at least 6 weeks. The subcutaneous injection of the hydrogel in a mouse animal model confirmed that the product physically provides a structure/space for at least 6 weeks post injection. As such, the results confirmed that the injected solution of aqueous PPHO and/or PPHO forms a hydrogel at body temperature at the point of administration to generate space to (i) reduce the effect of therapeutic radiation on the surrounding tissues; (ii) to fill a gap to reduce/normalise air pockets and therefore to enhance the accuracy of dose calculation; and (iii) to protect tissues, e.g., dermal, against direct radiation exposure.

[0128] *Figure 3* shows ultra-sound measurement of the injected hydrogels after injection. The results confirmed clear visualisation of the hydrogels at the administration site. The measurements were completed and the calculated volume of the hydrogel (~0.27 mL) was similar to the actual injected volume (0.25 mL). Distance 1 = 9.9 mm; distance 2 = 5.1 mm; and distance 3 = 10.3 mm; the calculated volume = 0.27 mL.

[0129] *Figure 4* shows the Hounsfield Unit output of TL150-IOPXX (defined below) in a subcutaneous injection model. *Figure 4a* is for TL150-IOP20 (i.e., 20 mg I/mL iohexol in 150 mg/mL PPHO); and *Figure 4b* is for TL150-IOP40 (i.e., 40 mg I/mL iohexol in 150 mg/mL PPHO). The results confirm that PPHO formulations in iohexol are radiopaque.

[0130] *Figure 5* shows the visibility of the product during and after gelation (confirmed via top up, increasing the initial volume of the product injection) via TRUS (Transrectal Ultra Sound) visibility upon gelation of TL150-IOP40 (i.e., 40 mg I/mL iohexol in 150 mg/mL PPHO).

[0131] *Figure 6* shows volume formation after gelation, with visibility under CT. Spacer spans of 13.7 mm (487 HU) and 11.85 mm (385 HU) were observed.

[0132] *Figure 7* shows space generation at the injection site following hydrodissection and 2 x 6 mL injection of TL150-IOP40.

Detailed Description of the Embodiments

[0133] The present invention will now be more fully described with reference to the accompanying examples and drawings. It should be understood, however, that the description following is illustrative only and should not be taken in any way as a restriction on the generality of the invention described above.

[0134] Reference will now be made in detail to certain embodiments of the invention. While the invention will be described in conjunction with the embodiments, it will be understood that the intention is not to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents, which may be included within the scope of the present invention as defined by the claims.

[0135] One skilled in the art will recognise many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. The present invention is in no way limited to the methods and materials described.

[0136] It will be understood that the invention disclosed and defined in this specification extends to all alternative combinations of two or more of the individual features mentioned or evident from the text or drawings. All of these different combinations constitute various alternative aspects of the invention.

[0137] Disclosed broadly herein is the use of a biocompatible polymer for administration to a treatment site at or proximal with a target tissue (*e.g.*, the human prostate), the polymer thereby forming a hydrogel at body temperature to provide physical spacing between the tissue and nearby cells/tissues/organs (*e.g.*, the human rectum). Such physical spacing/isolation of the prostate from the rectum allows radiation therapy to focus on the isolated target tissue without substantially affecting the cells/tissues/organs spaced from it by the polymer hydrogel.

Polymers

[0138] The term “polymer”, as used herein, refers to a large molecule (macromolecule) composed of repeating structural units (monomers). These subunits are typically connected

by covalent chemical bonds. Polymers can be linear or branched polymers. Preferably, the polymers of the present invention are copolymers comprising three or more different monomers. For example, in one embodiment, the polymer of the present invention includes a first water-binding monomer, a second monomer that is capable of imparting mechanical properties to the polymer, and a third monomer that has a functional group for binding to an NSPP.

[0139] The term “monomer”, as used herein, refers to a structural unit that can be combined to form a polymer, but that itself may also be a polymer, or a derivative of a monomer or polymer. Monomers of this type are herein also referred to as “macromonomers”. Herein, a “macromonomer” is a polymer or oligomer the molecules of which each have one end-group that acts as a monomeric molecule, so that each polymer or oligomer molecule contributes only a single monomer unit to a chain of the product polymer.

[0140] The polymer of the present invention comprises: a first monomer for binding water; a second monomer for imparting mechanical properties to the polymer; an optional third monomer for binding to a natural or synthetic peptide or protein (NSPP); and a fourth monomer for imparting phase-transition behaviour.

First monomer: Water-binding monomer

[0141] As discussed above, the advantages of the polymer of the present invention can be attributed, at least in part, to the particular components that make up the polymers of the present invention. A particularly advantageous property of the polymers of the present invention is their water-binding capacity. The presence of water in the polymer of the present invention provides an environment that resembles both that of the natural environment of the damaged tissue (which assists in tissue regeneration) and the required compression resistance to the polymer.

[0142] Accordingly, the preferred polymers used herein should include monomers or units that are able to bind water to such a capacity that a malleable structure is able to form when the polymer is hydrated. In addition, the structure thus formed should have the required compression resistance and resilience.

[0143] A person skilled in the art will understand that water-binding monomers need to be present in the polymers of the present invention in proportions that are sufficient to produce a polymer that fulfils these requirements. Generally, the proportion of water-binding monomers in the polymer is about 3:1, about 2:1, about 1:1, about 1:2, about 1:3,

about 1:4, about 1:5, about 1:10, about 1:20, about 1:30, about 1:40, about 1:50 molar ratio of water binding:mechanical strength monomers. In fact, the water-binding monomers need to make the polymer not only hydrophilic, but impart much more significant water-binding capacities to the polymer. Accordingly, polymers in accordance with the present invention will have water-binding capacities of between about 70% and about 500%, between about 80% and about 400%, between about 90% and 300% or between about 100% and 200%. For example, the water-binding capacity of the polymers of the present invention is about 70%, about 80%, about 90%, about 100%, about 110%, about 120%, about 130%, about 140%, about 150%, about 160%, about 170%, about 180%, about 190%, about 200%, about 210%, about 220%, about 230%, about 240%, about 250%, about 260%, about 270%, about 280%, about 290%, about 300%, about 310%, about 320%, about 330%, about 340%, about 350%, about 360%, about 370%, about 380%, about 390%, about 400%, about 410%, about 420%, about 430%, about 440%, about 450%, about 460%, about 470%, about 480%, about 490%, or about 500%.

[0144] Suitable examples of water-binding monomers include those that can be synthesised into polymers such as polyethers (*e.g.*, alkylene polyoxides such as polyethylene glycol (PEG), oligo(ethylene glycol) (OEG), polyethylene oxide (PEO), polyethylene oxide-co-propylene oxide (PPO), co-polyethylene oxide block or random copolymers, polyvinyl alcohol (PVA)), poly(vinyl pyrrolidinone) (PVP), poly(amino acids) and dextran. The polyethers, and more particularly oligo(oxyalkylenes) (*e.g.*, OEG), are especially preferred, because they have the requisite water-binding capacity, are simple to synthesise and/or purchase, and are inert, in the sense that they illicit minimal or no immune response from the tissues into which they are placed.

[0145] In addition, any of a variety of hydrophilic functionalities can be used to make a monomer (and therefore a polymer formed from such a monomer) water soluble. For example, functional groups like phosphate, sulphate, quaternary amine, hydroxyl, amine, sulfonate and carboxylate, which are water soluble, may be incorporated into a monomer to make it water soluble.

[0146] Monomers may also be reacted with other compounds to form “macromonomers”. Thus, the first monomer may optionally be a macromonomer.

[0147] A preferred first monomer which is a macromonomer is oligo(ethyleneglycol) monomethyl ether methacrylate (OEGMA), which is a hydrophilic monomer composed of two hydrophilic monomers: ethylene glycol and methacrylate.

[0148] Preferably, the polymer comprises the first monomer in an amount of from about 1

to about 15 mol%. In various embodiments, the first monomer may be present in about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, or about 15 mol%. In various embodiments, the first monomer may be present from about 1 to about 15, about 2 to about 14, about 3 to about 13, about 4 to about 12, about 5 to about 11, about 6 to about 10, about 7 to about 9, or about 8 mol%.

Second monomer: Monomer imparting mechanical properties

[0149] As discussed above, the advantageous properties of the polymer of the present invention can be attributed, in part, to the particular components that make up the polymers of the present invention. In some embodiments, the polymers of the present invention are able to contribute additional mechanical properties and adhesivity to the polymer of the present invention.

[0150] A person skilled in the art will understand that monomers capable of imparting mechanical properties to a polymer need to be present in the polymers of the present invention in proportions that are sufficient to produce a polymer having the desired mechanical properties. Generally, the proportion of “mechanical” monomers in the polymer is about 3:1, about 2:1, about 1:1, about 1:2, about 1:3, about 1:4, about 1:5, about 1:10, about 1:20, about 1:30, about 1:40, about 1:50 molar ratio of water binding:mechanical strength monomers. Suitable examples of monomers that are capable of imparting mechanical properties (e.g. compression resistance) to a polymer include acrylates such as hydroxyethyl methacrylate (HEMA), polyesters such as poly(lactic acid), poly(caprolactone), poly(glycolide), and their random co-polymers (e.g. poly(glycolide-co-lactide) and poly(glycolide-co-caprolactone)).

[0151] Monomers may also be reacted with other compounds to form “macromonomers”. A preferred second monomer which is a macromonomer is hydroxyethyl methacrylate poly(lactic acid) (PLA/HEMA).

[0152] Preferably, the polymer comprises the second monomer in an amount of from about 1 to about 50 mol%. In various embodiments, the second monomer may be present in about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, about 30, about 31, about 32, about 33, about 34, about 35, about 36, about 37, about 38, about 39, about 40, about 41, about 42, about 43, about 44, about 45, about 46,

about 47, about 48, about 49, or about 50 mol%.

[0153] In various embodiments, the second monomer may be present from about 1 to about 15, about 2 to about 49, about 3 to about 48, about 4 to about 47, about 5 to about 46, about 6 to about 45, about 7 to about 44, about 8 to about 43, about 9 to about 42, about 10 to about 41, about 11 to about 40, about 12 to about 39, about 13 to about 38, about 14 to about 37, about 15 to about 36, about 16 to about 35, about 17 to about 34, about 18 to about 33, about 19 to about 34, about 20 to about 33, about 21 to about 30, about 22 to about 29, about 23 to about 28, about 24 to about 27, or about 25 to about 26 mol%.

[0154] A person skilled in the art would understand that the amount of the second monomer occupies a broader range than the other monomers as mechanical strength and adhesivity are the critical factors in the present invention.

Third monomer: NSPP-binding monomer

[0155] As discussed above, the polymer used in the present invention can optionally be formed by combining the polymer with an NSPP. In order to effectively combine the polymer with the NSPP, preferably monomers or units that have a crosslinking ability are included in the polymer.

[0156] This crosslinking ability means that the polymers are able to bind to NSPPs and, by doing so, crosslink the NSPP to form polymer containing the NSPP. Alternatively, via a similar mechanism, the NSPPs act as the crosslinker, thereby crosslinking the polymer to form a polymer.

[0157] In order to produce a polymer that is capable of binding to NSPPs, a person skilled in the art will understand that monomers capable of binding to an NSPP need to be present in the polymers of the present invention in proportions that are sufficient to crosslink with an NSPP, such that a polymer can be formed in the presence of water. Generally, the proportion of “crosslinking” monomers in the polymer is at about 15:1, about 10:1, about 5:1, about 4:1, about 3:1, about 2:1, about 1:1, about 1:2, about 1:3, about 1:4, about 1:5, about 1:10, about 1:15 of crosslinking monomer:water binding monomer.

[0158] Monomers that are capable of binding to NSPPs generally have either electrophilic or nucleophilic functional groups, such that a nucleophilic functional group on, for example, an NSPP may react with an electrophilic functional group on the monomer, to form a covalent bond.

[0159] Therefore, for example, if an NSPP has nucleophilic functional groups such as amines, the polymer may have electrophilic functional groups such as N-

hydroxysuccinimides (NHS). Other electrophilic functional groups that are suitable for use in the present invention are N-hydroxysulfosuccinimide (SNHS) and N-hydroxyethoxylated succinimide (ENHS). An example of a monomer of this type is N-acryloxysuccinimide (NAS). On the other hand, if an NSPP has electrophilic functional groups, then the polymer may have nucleophilic functional groups such as amines or thiols.

[0160] Preferably, the polymer comprises the third monomer in an amount of up to 15 mol%. In various embodiments, the third monomer may be present in about 0, about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, or about 15 mol%. In various embodiments, the third monomer may be present from about 0 to about 1, about 1 to about 15, about 2 to about 14, about 3 to about 13, about 4 to about 12, about 5 to about 11, about 6 to about 10, about 7 to about 9, or about 8 mol%.

[0161] A skilled person would understand that the polymer may be formed from hydrophobic compositions, therefore the third monomer is optional in the polymer.

Fourth monomer: Phase-transition monomer

[0162] In another embodiment of the present invention, the polymer may further include a fourth monomer that is capable of imparting phase transition characteristics to the polymer, thereby ensuring post-administration stability of the polymer. Further, these phase-transition characteristics allow the polymers of the present invention to form polymer, of which various properties (such as viscosity) can be varied by altering factors such as pH and temperature. The polymers are designed such that the lower critical solution temperature (LCST) is below body temperature. Various thermo-responsive and injectable polymers including poly(ethylene oxide)/poly(propylene oxide) and poly(N-isopropylacrylamide) (PNIPAAm) copolymers are suitable for use in the present invention.

[0163] Generally, the proportion of phase-transition monomers in the polymer is at least about 3:1 molar ratio of phase-transition monomer:water binding monomer. This ratio can increase to, for example, about 10:1, about 11:1, about 12:1, about 13:1, about 14:1, about 15:1, about 16:1, about 17:1, about 18:1, about 19:1, about 20:1, about 25:1, about 30:1, about 35:1, about 40:1, about 45:1, about 50:1, about 55:1, about 60:1, about 65:1, about 70:1 molar ratio, about 75:1, about 80:1 and about 85:1 of phase-transition monomer:water binding monomer.

[0164] Preferably, the polymer comprises the fourth monomer in an amount which makes

up the remainder to 100% of the polymer composition. In an embodiment, the mol% of the fourth monomer can be up to about 85%, preferably, about 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84 or 85 mol%.

Other polymer properties

[0165] It will be understood by a person skilled in the art that, by combining different types of monomers, polymers can be produced that have a range of different properties. In addition, by incorporating particular monomers or functional groups into a pre-existing polymer, the properties of the polymer can be modified. For example, co-polymerisation of HEMA monomers with other monomers (such as methyl methacrylate) can be used to modify properties such as swelling and mechanical properties. Monomers may also be reacted with other compounds to form macromonomers (defined above) that are then included in the polymers of the present invention. For example, HEMA can be reacted with lactide to form a HEMA-poly-lactic acid polymer (PLA/HEMA), which itself can be used as a monomer in the polymers of the present invention. In addition, the monomers themselves may be combinations of monomer units, which are then incorporated into the polymer. An example of this type of monomer is oligo(ethylene glycol) monomethyl ether methacrylate (OEGMA), which is a hydrophilic monomer composed of two hydrophilic monomers: ethylene glycol and methacrylate.

[0166] The preferred polymers of the present invention may be further modified with one or more moieties and/or functional groups. Any moiety or functional group can be used in accordance with the present invention. In some embodiments, polymers may be modified with polyethylene glycol (PEG), with a carbohydrate, and/or with acyclic polyacetals derived from polysaccharides. In addition, as discussed above, hydrophilic groups can be incorporated into monomers (and therefore polymers) to increase the water-binding capacity of the polymer.

[0167] In terms of sequence, copolymers may be block copolymers, graft copolymers, random copolymers, blends, mixtures, and/or adducts of any of the foregoing and other polymers. Typically, polymers in accordance with the present invention are organic polymers. Preferably, the polymers of the present invention are biocompatible. In some embodiments, the polymers are biodegradable. In other embodiments, the polymers are both biocompatible and biodegradable.

[0168] The preferred polymers of the present invention may also include other monomers

in their structure. For example, the monomers may be polymers such as poly(vinyl alcohol) (PVA), polyesters, acrylic polymers and ionic polymers, or monomers of these.

[0169] If it is desired that the polymer be biodegradable or absorbable, one or more monomers having biodegradable linkages may be used. In the alternative, or in addition, the monomers may be chosen such that the product of the reaction between them results in a biodegradable linkage. For each approach, monomers and/or linkages may be chosen such that the resulting biodegradable polymer will degrade or be absorbed in a desired period of time, *e.g.*, from about 6 h to about 6 months. Preferably, the monomers and/or linkages are selected such that, when the polymer degrades under physiological conditions, the resulting products are non-toxic.

[0170] The biodegradable linkage may be chemically or enzymatically hydrolysable or absorbable. Illustrative chemically-hydrolysable biodegradable linkages include polymers, copolymers and oligomers of glycolide, lactide, caprolactone, dioxanone, and trimethylene carbonate. Illustrative enzymatically-hydrolysable biodegradable linkages include peptidic linkages cleavable by metalloproteinases and collagenases. Additional illustrative biodegradable linkages include polymers and copolymers of poly(hydroxy acid)s, poly(orthocarbonate)s, poly(anhydride)s, poly(lactone)s, poly(aminoacid)s, poly(carbonate)s, and poly(phosphonate)s.

[0171] The chemical hydrolysis of lactide in the invention results in the increase of lower critical solution temperature (LCST) of the polymer (by decreasing the overall hydrophobicity of the polymer) and thus its bioresorptive capacity.

Preferred polymers

[0172] The polymer preferably comprises the first monomer in an amount of from about 1 to about 15 mol%. In various embodiments, the first monomer may be present in about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, or about 15 mol%. Preferably, the first monomer is OEGMA.

[0173] The polymer preferably comprises the second monomer in an amount of from about 5 to about 50 mol%. In various embodiments, the second monomer may be present in about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, about 30, about 31, about 32, about 33, about 34, about 35, about 36, about 37, about 38, about 39, about 40, about 41, about 42, about 43, about 44, about 45, about 46,

about 47, about 48, about 49, or about 50 mol%. Preferably, the second monomer is PLA/HEMA.

[0174] The polymer preferably comprises the third monomer in an amount of up to 15 mol%. In various embodiments, the third monomer may be present in about 0, about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, or about 15 mol%. Preferably, the third monomer is NAS.

[0175] The polymer preferably comprises the fourth monomer in an amount which makes up the remainder to 100% of the polymer composition, for example, from about 50 and about 85 mol%. In an embodiment, the mol% of the fourth monomer can be up to about 85%, preferably, about 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84 or 85 mol%. Preferably, the fourth monomer is NIPAAm.

[0176] The percentages recited herein relate to the composition of the final polymer and not the feed amounts utilised when forming the polymer.

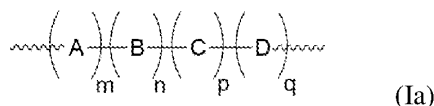
[0177] In one embodiment, the polymer preferably comprises: the first monomer in an amount of from about 1 to about 15 mol%; the second monomer in an amount of from about 5 to about 50 mol%; the third monomer in an amount of up to 15 mol%; and the fourth monomer in an amount of up to about 85 mol%.

[0178] Preferably, the first monomer is OEGMA, the second monomer is PLA/HEMA, the third monomer is NAS and the fourth monomer is NIPAAm.

[0179] In another embodiment, the polymer preferably comprises: the first monomer in an amount of about 7 mol%; the second monomer in an amount of about 30 mol%; the third monomer in an amount of about 7 mol%; and the fourth monomer in an amount of about 53 mol%.

[0180] Preferably, the first monomer is OEGMA, the second monomer is PLA/HEMA, the third monomer is NAS and the fourth monomer is NIPAAm.

[0181] In one embodiment, the polymer of the present invention is a polymer of formula (Ia):



[0182] wherein

[0183] A is the first monomer (a water-binding monomer), for example, OEGMA;

[0184] B is the second monomer (a monomer that is capable of imparting mechanical

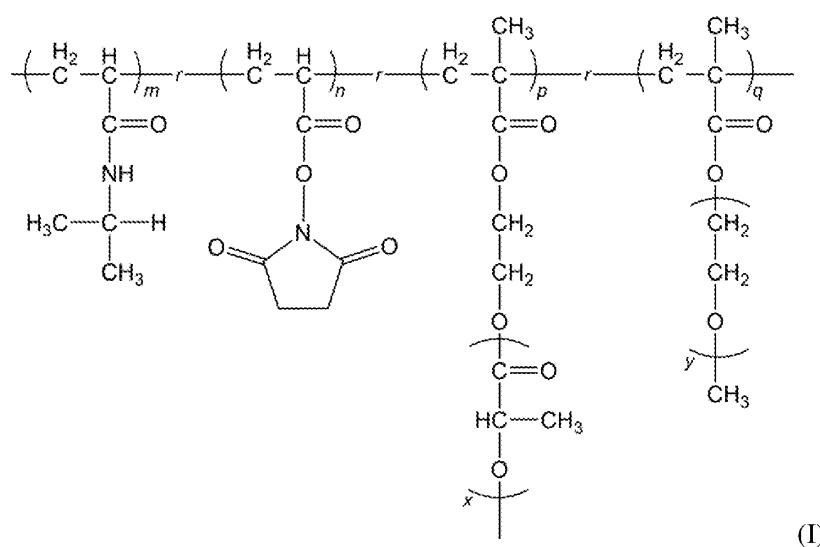
properties to a polymer), for example, PLA/HEMA;

[0185] C is the third monomer (a monomer that has a functional group for binding to an NSPP), for example, NAS; and

[0186] D is the fourth monomer (a monomer that is capable of imparting phase transition characteristics to the polymer), for example, NIPAAm.

[0187] In various embodiments, m is an integer from 1 to 20; n is an integer from 1 to 20; p is an integer from 0 to 20; and q is an integer from 1 to 20.

[0188] An exemplary polymer of the present invention is represented by Formula (I), below:



[0189] wherein A is the water-binding monomer OEGMA, B is the strengthening monomer PLA/HEMA, C is the crosslinker NAS, D is the phase transition monomer NIPAAm, and m, n and p, q, x and y are as defined above.

[0190] A person skilled in the art will be aware that the monomers A, B, C and D may be present in the polymer in any order, provided that the required water-binding, strengthening and/or cross-linking capabilities are achieved.

[0191] It has also been discovered that some monomers, such as PLA/HEMA, polyesters such as poly(lactic acid), poly(caprolactone), poly(glycolide), and their random copolymers (*e.g.*, poly(glycolide-co-lactide) and poly(glycolide-co-caprolactone) and other biodegradable and biocompatible polymers, can elevate the LCST of the preferred polymer used in the present invention during degradation of biodegradable segments (*e.g.*, PLA) *in vivo*, leading to bioresorption of the polymer. This provides the additional advantage that the polymers used in the present invention may be designed so as to be

biodegradable *in vivo*.

[0192] The overall size of the preferred polymer used in the present invention may differ, depending on factors such as the types of monomers that are incorporated into the polymer, the type of NSPP that is sought to be used to form the polymer, and the conditions under which the protein is to be coupled to the polymer. However, in general, the preferred polymer used in the present invention may be a molecule of about 1 to about 100 kDa, about 5 to about 60 kDa, or about 30 kDa. In various embodiments, the polymer of the present invention may be a molecule of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or about 100 kDa.

PNPHO, e.g., Formula (I)

[0193] A preferred polymer of the present invention is Poly(NIPAAm-*co*-NAS-*co*-(PLA/HEMA)-*co*-OEGMA), *i.e.*, “PNPHO”. The polymer PNPHO preferably comprises OEGMA in an amount of from about 1 and about 15 mol%, PLA/HEMA in an amount of from about 5 and about 50 mol%, NAS in an amount of up to 15 mol%, and NIPAAm in an amount which makes up the remainder to 100% of the polymer composition, for example, from about 50 to about 85 mol%.

[0194] The percentages recited herein relate to the composition of the final polymer and not the feed amounts utilised when forming the polymer.

[0195] In one embodiment, preferably the polymer comprises:

[0196] OEGMA in an amount of from about 3 to about 8 mol% (for example from about 4 to about 6 mol%);

[0197] HEMA-PLA in an amount of from about 5 to about 9 mol% (for example from about 6 to about 8 mol%);

[0198] NAS in an amount of at least about 7 mol%; and

[0199] NIPAAm in an amount of up to about 85 mol% (for example up to about 81 mol%).

[0200] In another embodiment, the polymer comprises:

[0201] OEGMA in an amount of about 5 mol%;

[0202] HEMA-PLA in an amount of about 7 mol%;

[0203] NAS in an amount of about 7 mol%; and

[0204] NIPAAm in an amount of about 81 mol%.

[0205] A preferred form of the polymer PNPFO for use in the present application is a polymer of Formula (I), as drawn above.

[0206] Based on Formula I, defined previously:

[0207] A is oligo (ethylene) glycol monomethyl ether methacrylate OEGMA;

[0208] B is hydroxyethyl methacrylate poly(lactic acid) (HEMA-PLA);

[0209] C is N-acryloxysuccinimide (NAS); and

[0210] D is N-isopropylacrylamide (NIPAAm).

[0211] A preferred form of the polymer PNPFO for use in the present application is a polymer of Formula (I), as drawn above. In addition, x is in the range of 1-1000 and y is in the range of 1-1000 and m, n, p, and q are in the range of 1-20.

[0212] A person skilled in the art will be aware that the monomers A, B, C and D may be present in the polymer in any order, provided that the required water-binding, strengthening and/or cross-linking capabilities are achieved.

PPHO, e.g., Formula (II)

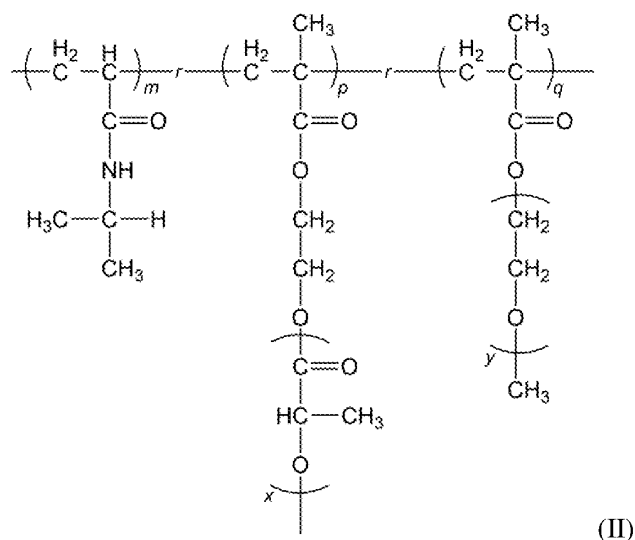
[0213] Another preferred polymer of the present invention is Poly(NIPAAm-co-(PLA/HEMA)-co-OEGMA), *i.e.*, "PPHO". The polymer PPHO preferably comprises OEGMA in an amount of from about 1 and about 15 mol%, PLA/HEMA in an amount of from about 5 and about 50 mol%, and NIPAAm in an amount which makes up the remainder to 100% of the polymer composition, for example, from about 50 to about 85 mol%. In preferred embodiments, PPHO comprises OEGMA in about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or about 15 mol% and/or PLA/HEMA in about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49 or about 50 mol% and/or NIPAAm in an amount of about 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84 or about 85 mol%.

[0214] The percentages recited herein relate to the composition of the final polymer and not the feed amounts utilised when forming the polymer.

[0215] A preferred form of the polymer PPHO for use in the present application is a polymer of Formula (II), as drawn below. In addition, x is in the range of 1-1000 and y is in the range of 1-1000 and m, n, and q are in the range of 1-20.

[0216] A person skilled in the art will be aware that the monomers A, B, and D may be present in the polymer in any order, provided that the required water-binding,

strengthening and/or cross-linking capabilities are achieved.



Synthesis of polymers

[0217] A person skilled in the art will be aware of suitable methods of synthesising the preferred polymers used in the present invention. These include methods such as ring-opening polymerisation, addition polymerisation (including free radical polymerisation) and condensation polymerisation.

[0218] The formation of the preferred polymers, PNPFO and PPHO, is described in the examples below.

Excipients and biologically-active agents

[0219] Pharmaceutically-acceptable excipients may be included in the compositions and/or polymer of the present invention, and include any and all solvents, dispersion media, inert diluents, or other liquid vehicles, dispersion or suspension aids, granulating agents, surface active agents, disintegrating agents, isotonic agents, thickening or emulsifying agents, preservatives, binding agents, lubricants, buffering agents, oils, and the like, as suited to the particular dosage form desired. Remington (Gennaro, A. R., Remington: The Science and Practice of Pharmacy, 21st Ed (2006) Lippincott Williams & Wilkins) discloses various excipients used in formulating pharmaceutical compositions and known techniques for the preparation thereof. Except insofar as any conventional excipient is incompatible with a substance or its derivatives, such as by producing any undesirable biological effect

or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition, its use is contemplated to be within the scope of this invention.

[0220] Excipients such as colouring agents, coating agents, sweetening, flavouring, and perfuming agents can be present in the composition, according to the judgment of the formulator.

[0221] Biologically active agents or drug compounds that may be added to the composition and/or polymer of the present invention include proteins, glycosaminoglycans, carbohydrates, nucleic acids and inorganic and organic biologically active compounds, such as enzymes, antibiotics, anti-neoplastic agents, local anaesthetics, hormones, angiogenic agents, anti-angiogenic agents, growth factors (*e.g.*, insulin-like growth factor-1 (IGF-1), basic fibroblast growth factor (bFGF) and transforming growth factor- β (TGF β)), antibodies, neurotransmitters, psychoactive drugs, anticancer drugs, chemotherapeutic drugs, drugs affecting reproductive organs, genes, and oligonucleotides.

[0222] A composition containing components such excipients and/or biologically active agents can be produced by combining a polymer of the present invention with an NSPP, combining this with one or more other components and then freeze-drying the resulting composition. This leads to a ready to use polymer.

[0223] The amount of polymer, NSPP and biologically active agent present in the composition will necessarily depend upon the particular drug and the condition to be treated. A person skilled in the art will be aware of appropriate agents and amounts to use to treat the condition.

Compositions for forming hydrogels

[0224] The present invention also relates to a preferred composition useful for forming a hydrogel for use in the invention.

[0225] The composition of the present invention comprises a polymer and optionally an NSPP, the polymer comprising:

[0226] a first water-binding monomer; and

[0227] a second monomer that imparts mechanical properties;

[0228] optionally, a third monomer that is an NSPP-binding monomer, comprising a functional group that is capable of binding to the NSPP;

[0229] a fourth monomer capable of imparting phase transition characteristics to the hydrogel;

[0230] wherein the natural or synthetic peptide or protein (NSPP) may be Thymosin beta-4 or a functional homolog thereof;

[0231] and wherein the binding of the NSPP to the second monomer crosslinks the polymer, thereby enabling formation of a hydrogel when the composition is contacted with water.

[0232] The term “composition”, as used herein, refers to a solid or liquid composition containing the components mentioned above. In some embodiments, other components such as pharmaceutically-acceptable excipients and biologically active agents (*e.g.*, drugs, vitamins and minerals), to assist in repair and/or re-generation of the target bone tissue, and/or to provide a method of achieving targeted delivery of biologically active compounds, may also be included in the preferred compositions used in the present invention.

[0233] In general, the amount of polymer in the composition used in the present invention is an amount that allows for the formation of hydrogels.

[0234] In some embodiments, the amount of polymer in the composition ranges: from about 1% w/w to about 90% w/w, from about 2% w/w to about 80% w/w, from about 4% w/w to about 70% w/w, from about 5% w/w from about 60% w/w, from about 5% w/w to about 50% w/w, from about 6% w/w to about 40% w/w, from about 7% w/w to about 30% w/w or from about 8% w/w to about 20% w/w.

[0235] In some embodiments, the amount of polymer is: about 1% w/w, about 2% w/w, about 3% w/w, about 4% w/w, about 5% w/w, about 6% w/w, about 7% w/w, about 8% w/w, about 9% w/w, about 10% w/w, about 15% w/w, about 20% w/w, about 25% w/w, about 30% w/w, about 35% w/w, about 40% w/w, about 45% w/w, about 50% w/w, about 55% w/w, about 60% w/w, about 65% w/w, about 70% w/w, about 75% w/w, about 80% w/w or more. In some embodiments, the amount of polymer is approximately 85% w/w.

[0236] As a general rule, the solidity of the hydrogel increases with higher polymer concentrations in the composition.

[0237] In general, the amount of NSPP in the composition of the present invention is an amount that allows for the formation of hydrogels.

[0238] In some embodiments, the amount of NSPP in the composition ranges: from about 0.01% w/w to about 60% w/w, from about 1% w/w to about 50% w/w, from about 1% w/w to about 40% w/w, from about 5% w/w to about 30% w/w, from about 5% w/w to about 20% w/w, or from about 5% w/w to about 10% w/w.

[0239] In some embodiments, the percent of NSPP is about 1% w/w, about 2% w/w, about

3% w/w, about 4% w/w, about 5% w/w, about 6% w/w, about 7% w/w, about 8% w/w, about 9% w/w, about 10% w/w, about 20% w/w, about 30% w/w, about 40% w/w, about 50% w/w, or more.

[0240] The % w/w is based on the total weight of the composition before the composition is contacted with water.

Detailed Description of a Preferred Embodiment

Use of PNPFO/PPHO as an oncological spacer

[0241] As noted above, the present invention relates to administering a polymer to a treatment site at or proximal with a target tissue (*e.g.*, the human prostate), the polymer thereby forming a hydrogel at body temperature to provide physical spacing between the tissue and nearby cells/tissues/organs (*e.g.*, the human rectum). Such physical spacing/isolation of the prostate from the rectum allows radiation therapy to focus on the isolated target tissue without substantially affecting the cells/tissues/organs spaced from it by the polymer hydrogel.

[0242] The polymer is preferably Poly(N-isopropylacrylamide-*co*-(N-acryloxysuccinimide)-*co*-(polylactide/2-hydroxy methacrylate)-*co*-(oligo (ethylene glycol) / Poly(NIPAAm-*co*-NAS-*co*-(PLA/HEMA)-*co*-OEGMA), *i.e.*, PNPFO.

[0243] The polymer is alternatively Poly(N-isopropylacrylamide-*co*-(polylactide/2-hydroxy methacrylate)-*co*-(oligo (ethylene glycol) / Poly(NIPAAm-*co*-(PLA/HEMA)-*co*-OEGMA), *i.e.*, PPHO.

[0244] The present inventors have surprisingly found that at concentrations above about 100 mg/mL in aqueous solution, PNPFO and/or PPHO can be administered (preferably via injection) at or near a cancerous organ (*e.g.*, prostate) to form a hydrogel that provides physical spacing between the tissue and nearby cells/tissues/organs (*e.g.*, rectum). Such physical spacing/isolation of the prostate from the rectum allows radiation therapy to focus on the isolated target tissue without substantially affecting the cells/tissues/organs spaced from it by the polymer hydrogel.

[0245] The injected solution of aqueous PNPFO and/or PPHO forms a hydrogel at the body temperature that has a CT-Hounsfield Unit of between 10 and 60 (HU) which is similar to water to soft tissue equivalent and therefore suitable to guarantee precise radiation oncology by obtaining the relationship between HU and electron densities of the structures exposed to radiation beams.

[0246] The injected solution of aqueous PNPFO and/or PPHO forms a hydrogel at body

temperature at the point of administration to generate space to (i) reduce the effect of therapeutic radiation on the surrounding tissues; (ii) to fill a gap to reduce/normalise air pockets and therefore to enhance the accuracy of dose calculation; and (iii) to protect tissues, *e.g.*, dermal, against direct radiation exposure.

[0247] In one form, the injected solution of aqueous PHPHO and/or PPHO can be injected between a human rectum and prostate to provide a temporary space between the organs to reduce the delivered dose of radiation to the rectum where the prostate is targeted for radiotherapy.

[0248] In another form, the injected solution of aqueous PHPHO and/or PPHO can be used to fill the defect site after a cancer surgery, *e.g.*, tumour resection, to reduce air pockets at the site and thus to enhance the accuracy of the electron density map.

[0249] In another form, the solution of aqueous PHPHO and/or PPHO can cover a dermal surface layer (in either injectable and/or pliable form) to cover skin/dermal tissue to prevent direct exposure and thus reduce pigmentation during radiation.

[0250] In an experiment, “TP280” (280 mg/mL of PNPCHO in aqueous solution) was tested in a radiation oncology CT simulation to acquire its Hounsfield (or CT) number.

Hounsfield values are the basic input for radiotherapy planning systems which consider tissue heterogeneities. The results showed that the Hounsfield value of TP280 was less than 50, which is comparable to that of soft tissue and therefore suitable to generate space between different organs and/or to fill a site to reduce air pockets.

[0251] In addition, the homogeneity of the TP280 hydrogel product under the simulation confirms its potential application to fill a gap for more accurate mapping.

[0252] The solution of aqueous PHPHO and/or PPHO can be applied via direct injection to the site. After gelation, triggered by temperature, the resulting hydrogels provide sufficient mechanical/structural stability to generate space and under simulated radiation CT and provide a homogenous structure for relatively accurate radiation.

Use of PNPCHO/PPHO as a hydrodissection tool

[0253] As noted above, the present invention relates to administering a polymer as a non-irritant solution, visible with ultrasound for accurate hydrodissection (*e.g.*, for perirectal fat). Such hydrodissection solution allows accurate injection of the solution to prevent side effects such as rectal wall infiltration in the application of spacers. Alternatively, the polymer/s of the invention can be used as a space filler to reduce the presence of air pocket/air cavity in target radiation therapy (*e.g.*, after lumpectomy and MammoSite

treatment). Such hydrogel filler to remove air pockets/cavities can reduce the heterogeneity of the air pockets/cavities in targeted radiation therapy (*e.g.*, MammoSite) and thus can reduce the dose errors to the tissue located near the air-tissue interface due to lack of attenuation and inverse square correction.

[0254] The polymer is preferably Poly(N-isopropylacrylamide-*co*-(N-acryloxysuccinimide)-*co*-(polylactide/2-hydroxy methacrylate)-*co*-(oligo (ethylene glycol) / Poly(NIPAAm-*co*-NAS-*co*-(PLA/HEMA)-*co*-OEGMA), *i.e.*, PNPFO.

[0255] The polymer is alternatively Poly(N-isopropylacrylamide-*co*-(polylactide/2-hydroxy methacrylate)-*co*-(oligo (ethylene glycol) / Poly(NIPAAm-*co*-(PLA/HEMA)-*co*-OEGMA), *i.e.*, PPHO.

[0256] The present inventors have surprisingly found that at concentrations between about 25 mg/mL and about 100 mg/mL in aqueous solution, PNPFO and/or PPHO can be administered (preferably via injection) at or near tissues otherwise earmarked for hydrodissection. Such an observation has two principal applications: 1) to be injected into a tissue to dissect the target tissue/s; and (2) to be visible under ultrasound and/or CT-scan for a more accurate needle placement/ hydrodissection.

[0257] The injected solution of aqueous PNPFO and/or PPHO forms a hydrogel at the body temperature that has a CT-Hounsfield Unit of between 10 and 60 (HU) which is similar to water and soft tissue equivalent.

[0258] In one form, the injected solution of aqueous PHPHO and/or PPHO can be injected into perirectal fat as an alternative to regular hydrodissection.

[0259] In an experiment, “TP50” (50 mg/mL of PNPFO in aqueous solution) was tested in the hydrodissection of perirectal fat.

[0260] The solution of aqueous PHPHO and/or PPHO can be applied via direct injection to the site. After gelation, triggered by temperature, the resulting hydrogels provide sufficient mechanical/structural stability to generate space and under simulated radiation CT and provide a homogenous structure for relatively accurate radiation.

Product Hounsfield units

[0261] Four formulations were formed, and their Hounsfield units were measured. The results are shown in *Table 1*.

[0262] The results confirmed that formulations with iohexol are radiopaque and return a Hounsfield number between about 100 and about 1000, demonstrating the modularity of the product. The products are coded as “IOPXX”, where XX represent the concentration of

iohexol in the final formulations. For example, IOP20 represents a formulation with 20 mg I/mL Iohexol in the final product.

Table 1. Hounsfield units of different TL150 formulations, formed with a wide range of iohexol contents

Product Code	Iohexol (mg I/mL)	HU	Reference
TL150-IOP20	20	241	Figure 4a
TL150-IOP40	40	350-500	Figure 4b
TL150-IOP60	60	634	-
TL150-IOP80	80	804	-

*TL150 = 150 mg/mL PPHO solution

Space generating and volume formation

[0263] In this investigation, TL150-IOP50 was confirmed as procedurally injectable through an 18G needle in 5 mL, 10 mL and Gamma variants.

[0264] Secondly, TRUS (Transrectal Ultra Sound) visibility upon gelation of TL150-IOP40 was confirmed at t=0 and t=10 min post initial implant. The extended t-outcome was confirmed at the time of top up injection (see, *Figure 5*).

[0265] Volume formation after gelation is shown in *Figure 6*, with visibility under CT.

Hydrodissection

[0266] In this investigation, a gap was formed via injection of 5 mL saline at the site (hydrodissection), prior to injection of TL150-IOP40.

[0267] Following the initial injection (6 mL), additional 6 mL of TL150-IOP40 was injected to confirm the optionality of the product (compatible with hydrodissection and multiple phases of injection).

[0268] The results in *Figure 7* confirm the formation of the product and space generation following hydrodissection and two injections (two separate sequences).

TRUS guided implant and anatomy nuances for porcine vs. human model

[0269] The anatomy of a porcine prostate/rectum model is more complex than that of a human, specifically as it relates to the perirectal space. A standard operating procedure was adapted from human to porcine model effectively. This provides confidence to prospective end users that the results and outcomes achieved by this study could be further improved in a human study model.

Preferred formula of TL150-IOP40 in 10 mL syringe

[0270] This study provided a good opportunity to test the functional parameters and design inputs of the injectable product. Finding the “sweet spot” involved the following considerations:

[0271] Ascertaining the highest TP or TL concentration consistently injectable through a non-pressurised, 18G x 150 mm needle.

[0272] TL concentrations of TL100 and TL200 were the test articles in a previous murine model for safety, efficacy and resorption. The results of that study were 6 and 10-weeks, respectively, before the measured resorption reduced the implant size below 100%. The selection of TL150 provides good potential to deliver an 8-week resorption result.

[0273] The results achieved provided assurance that 10 mL of TL150 should be sufficient to create an equivalent space to that required in a human model. The additional cost, plastic waste and internal pressure of larger syringes (e.g., 20 mL) was considered before deciding upon a standard device design at 10 mL. Additionally, it was observed to be infrequent that patients need more than 10 mL of a prostate spacer. However, if needed, the TL150 implant “top up” has been confirmed as possible through this study.

Transrectal ultrasound (TRUS) visibility

[0274] TRUS visibility was very good for each of the specimens on which it was used. This is important for both safety and efficacy for perirectal spacing. Visibility is important for a proceduralist to reduce the risk of human error associated with needle insertion and placement during the procedure. Ultrasound visibility also ensures that the proceduralist can review, in real time, the placement and profile of the spacer, reducing the risk of poor implant outcomes through the inability to “top up” or sculpt the spacer implant to rectify the initial placement. Two points are worth noting as it relates to the predicate devices: SpaceOar Vue (Boston Scientific) has poor (to no) visibility on TRUS once the hydrogel has formed; and comparable visibility to Barrigel (Teleflex) which similarly allows for more procedure flexibility.

Ambient temperature management

[0275] Previous bench testing of the product leading up to this study informed a hypothesis that TL150-IOP40 has the potential to be managed at closer to ambient temperature. The testing completed and outcomes observed informed an immediate

recommendation that temperature strips be added to commercial packaging, along with formal storage and shelf testing to validate the temperature.

Industrial Applicability

[0276] It will be appreciated that the present invention finds ready applicability in the biomedical, surgical and therapeutic fields. The biocompatible PNPFO or PPHO polymers in aqueous solution provide for administration, preferably via injection, at a treatment site to form a hydrogel to physically space/isolate target tissue for radiotherapy. For cancers such as prostate cancer, in which several unaffected organs/tissues (*e.g.*, bladder, rectum) may be in close proximity, it is clearly desirable to minimise their exposure to the radiation.

[0277] In respect of the first aspect of the invention the key findings of the present investigation were:

[0278] At concentrations above about 100 mg/mL, PNPFO and PPHO solutions in aqueous solution can be used to generate space between different organs for more targeted therapeutic radiation.

[0279] The injected solution forms a hydrogel at body temperature at the point of administration to generate space to reduce the effect of therapeutic radiation on the surrounding tissues; to fill a gap to reduce/normalise air pockets and therefore to enhance the accuracy of dose calculation; and to protect tissues, *e.g.*, dermal, against direct radiation exposure.

[0280] The solutions of the invention can be injected between a human rectum and prostate to provide a temporary space between the organs to reduce the delivered dose of radiation to the rectum where the prostate is targeted for radiotherapy.

[0281] The solutions of the invention can be used to fill the defect site after a cancer surgery, *e.g.*, tumour resection, to reduce air pockets at the site and thus to enhance the accuracy of the electron density map.

[0282] The solutions of the invention can cover a dermal surface layer (in either injectable and/or pliable form) to cover skin/dermal tissue to prevent direct exposure and thus reduce pigmentation during radiation.

[0283] In an experiment, “TP280” (280 mg/mL of PNPFO in aqueous solution) was tested in a radiation oncology CT simulation to acquire its Hounsfield (or CT) number. Hounsfield values are the basic input for radiotherapy planning systems which consider tissue heterogeneities.

[0284] The results showed that the Hounsfield value of TP280 was less than 50, which is comparable to that of soft tissue and therefore suitable to generate space between different organs and/or to fill a site to reduce air pockets.

[0285] In addition, the homogeneity of the TP280 hydrogel product under the simulation confirms its potential application to fill a gap for more accurate mapping.

[0286] The solutions of the invention can be applied via direct injection to the site. After gelation, triggered by temperature, the resulting hydrogels provide sufficient mechanical/structural stability to generate space and under simulated radiation CT and provide a homogenous structure for relatively accurate radiation.

[0287] A porcine cadaveric study confirms the design lock of TL150-IOP40 in a 10 mL Gamma sterilised syringe, for use in the first in human product feasibility sponsored study. A summary of the conclusions which informed this are:

[0288] TL150 is the highest polymer concentration to flow through a non-pressurised 18G x 150 mm needle when managed at the manufacturer recommended 2-8 degrees Celsius.

[0289] IOP40 is an optimal iodine concentration that is observed to not negatively impact the intended use performance of the biocompatible polymers of the invention and is measured to have Hounsfield Units under a design threshold of 1000.

[0290] TL150-IOP40 created the desired space, provides procedural optionality, and was visible under on CT plus TRUS – even post implant during a “top-up” injection.

[0291] Transrectal ultrasound guided insertions will be applicable and standard for the first in human use.

[0292] The procedural efficacy of the TL150-IOP40 product in the porcine model would also suggest that a commercial veterinary spacing product is a technically viable outcome.

[0293] Although the invention has been described with reference to specific examples it will be appreciated by those skilled in the art that the invention may be embodied in many other forms.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A polymer for administering at a treatment site to form a hydrogel to physically space/isolate target tissue for radiotherapy, the polymer comprising:
 - 5 a first monomer for binding water;
 - a second monomer for imparting mechanical properties;
 - optionally, a third monomer for binding to a natural or synthetic peptide or protein (NSPP); and
 - a fourth monomer for imparting phase-transition behaviour.
- 10 2. A polymer for administering at a treatment site to form a hydrogel to physically hydrodissect two or more abutting tissues, the polymer comprising:
 - a first monomer for binding water;
 - a second monomer for imparting mechanical properties;
 - 15 optionally, a third monomer for binding to a natural or synthetic peptide or protein (NSPP); and
 - a fourth monomer for imparting phase-transition behaviour.
- 20 3. A polymer according to claim 1 or claim 2, wherein the first monomer is selected from: polyethers, polyvinyl alcohol (PVA); poly(vinyl pyrrolidone) (PVP); poly(amino acids) and dextran.
- 25 4. A polymer according to claim 3, wherein the polyethers are selected from: polyethylene glycol (PEG), oligo(ethylene glycol) (OEG), polyethylene oxide (PEO), polyethylene oxide-co-propylene oxide (PPO), co-polyethylene oxide block or random copolymers thereof.
- 30 5. A polymer according to claim 4, wherein the first monomer is oligo (ethylene) glycol monomethyl ether methacrylate (OEGMA).
6. A polymer according to any one of the preceding claims, wherein the second monomer is a methacrylate, or a random co-polymer comprising a methacrylate.

7. A polymer according to claim 6, wherein the second monomer is selected from:
hydroxyethyl methacrylate (HEMA), a hydroxyethyl methacrylate poly(lactic acid)
copolymer (PLA/HEMA), poly(lactic acid), poly(caprolactone), poly(glycolide),
poly(glycolide-colactide) or poly(glycolide-co-caprolactone).
5
8. A polymer according to claim 7, wherein the second monomer is hydroxyethyl
methacrylate poly(lactic acid) (PLA/HEMA).
9. A polymer according to any one of the preceding claims, wherein the third monomer
10 has electrophilic functional groups for binding to the NSPP.
10. A polymer according to claim 9, wherein the third monomer is selected from: N-
hydroxysulfosuccinimide (SNHS), N-hydroxyethoxylated succinimide (ENHS), and
N-acryloxysuccinimide (NAS).
15
11. A polymer according to any claim 10, wherein the third monomer is N-
acryloxysuccinimide (NAS).
12. A polymer according to any one of the preceding claims, wherein the fourth
20 monomer has a lower critical solution temperature (LCST) less than about 37 °C.
13. A polymer according to claim 12, wherein the fourth monomer is selected from:
poly(ethylene oxide)/poly(propylene oxide) and poly(N-isopropylacrylamide)
(PNIPAAm) homopolymers and copolymers.
25
14. A polymer according to claim 13, wherein the fourth monomer is (N-
isopropylacrylamide) (NIPAAm).
15. A polymer according to any one of the preceding claims, wherein the polymer
30 comprises the first monomer in an amount of from about 1 to about 15 mol%.
16. A polymer according to any one of the preceding claims, wherein the polymer
comprises the second monomer in an amount of from about 5 to about 50 mol%.

17. A polymer according to any one of the preceding claims, wherein the polymer comprises the third monomer in an amount of from about 0 to about 15 mol%.
- 5 18. A polymer according to any one of the preceding claims, wherein the polymer comprises the fourth monomer in an amount of from about 50 to about 85 mol%.
- 10 19. A polymer according to any one of the preceding claims, wherein the polymer comprises: the first monomer in an amount of from about 1 to about 15 mol%; the second monomer in an amount of from about 5 to about 50 mol%; the third monomer in an amount of 0 to about 15 mol%; and the fourth monomer in an amount which makes up the remainder to 100% of the polymer.
- 15 20. A polymer according to any one of the preceding claims, wherein: the first monomer is OEGMA; the second monomer is PLA/HEMA; the third monomer is NAS; and the fourth monomer is NIPAAm,
wherein the polymer comprises: OEGMA in an amount of from about 1 to about 15 mol%; PLA/HEMA in an amount of from 5 to about 50 mol%; NAS in an amount of from 0 to about 15 mol%; and NIPAAm in an amount of up to about 85
20 mol%.
- 25 21. A polymer according to any one of claims 1 or claims 3 to 20, wherein to administer the polymer at the treatment site, it is dissolved or dispersed in aqueous solution at a polymer concentration greater than about 100 mg/mL.
22. A polymer according to claim 21, wherein to administer the polymer at the treatment site, it is dissolved or dispersed in aqueous solution at a polymer concentration of about 280 mg/mL.
- 30 23. A polymer according to claim 21 or claim 22, wherein the target tissue for radiotherapy is a human prostate gland.
24. A polymer according to claim 23, wherein administering the polymer at the

treatment site is performed by injection.

25. A polymer according to claim 24, wherein the polymer is injected between a patient's rectum and prostate to provide a temporary space between said organs,
5 thereby reducing the dosage of radiation delivered to the rectum.

26. A polymer according to any one of claims 2 to 20, wherein to administer the polymer at the treatment site, it is dissolved or dispersed in aqueous solution at a polymer concentration between about 25 mg/mL and about 100 mg/mL.
10

27. A polymer according to claim 26, wherein administering the polymer at the treatment site is performed by injection.

28. A polymer according to any one of the preceding claims, wherein
15 the first monomer is OEGMA; the second monomer is PLA/HEMA; the third monomer is NAS; and the fourth monomer is NIPAAm;

wherein the polymer comprises: OEGMA in an amount of from about 1 to about 15 mol%; PLA/HEMA in an amount of from 5 to about 50 mol%; NAS in an amount of from 0 to about 15 mol%; and NIPAAm in an amount of up to about 85
20 mol%;

wherein the target tissue for radiotherapy is a human prostate gland; and
wherein the polymer is present in a concentration of about 280 mg/mL.

29. A method for physically spacing/isolating a target tissue for radiotherapy, the
25 method comprising administering to a subject in need thereof an effective concentration of a polymer as defined according to any one of claims 1 or 3 to 25 at or proximal to the target tissue.

30. A method for physically hydrodissecting two or more abutting tissues at a treatment
30 site, the method comprising administering to a subject in need thereof an effective concentration of a polymer as defined according to any one of claims 2 to 20, 26 or 27 at or proximal to the treatment site.

31. A method according to claim 29 or claim 30, wherein the administration is performed at body temperature.
- 5 32. A method according to any one of claims 29 to 31, wherein the administration is performed by injection.
33. A method according to any one of claims 29 to 32, wherein the target tissue for radiotherapy is a human prostate gland.
- 10 34. A method according to any one of claims 29 to 33, wherein to administer the polymer at the treatment site, it is dissolved or dispersed in aqueous solution at a polymer concentration of about 280 mg/mL.
- 15 35. A method according to claim 34, wherein the polymer is injected between a patient's rectum and prostate to provide a temporary space between said organs, thereby reducing the dosage of radiation delivered to the rectum.
- 20 36. Use of a polymer as defined according to any one of claims 1 to 28 for physically spacing/isolating a target tissue for radiotherapy.
37. Use according to claim 36, wherein the administration is performed at body temperature.
- 25 38. Use according to claim 36 or claim 37, wherein the administration is performed by injection.
39. Use according to any one of claims 36 to 38, wherein the target tissue for radiotherapy is a human prostate gland.
- 30 40. Use according to any one of claims 36 to 39, wherein to administer the polymer at the treatment site, it is dissolved or dispersed in aqueous solution at a polymer concentration of about 280 mg/mL.

41. Use according to claim 40, wherein the polymer is injected between a patient's rectum and prostate to provide a temporary space between said organs, thereby reducing the dosage of radiation delivered to the rectum.

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42. A kit for physically spacing/isolating target tissue for radiotherapy, the kit comprising a polymer as defined according to any one of claim 1 to 28; means for administering said polymer; and instructions for administering said polymer at or proximal to said target tissue.