Abstract:
The present invention relates to a method of identifying a target area for delivery of a prophylactic or therapeutic operant and to methods of prophylaxis or treatment of a disease or treatment of trauma or for the induction of wellbeing. In particular, the invention relates to methods of prophylaxis or treatment of a disease or treatment of trauma by delivery of a therapeutic operant to a target area identified in the novel identification methods.
METHOD OF IDENTIFYING A TARGET AREA FOR DELIVERY OF A THERAPEUTIC OPERANT AND RELATED METHODS OF PROPHYLAXIS OR TREATMENT

5 FIELD OF THE INVENTION

The present invention relates to a method of identifying a target area for delivery of a prophylactic or therapeutic operant and to methods of prophylaxis or treatment of a disease or treatment of trauma or for the induction of wellbeing. In particular, the invention relates to methods of prophylaxis or treatment of a disease or treatment of trauma by delivery of a therapeutic operant to a target area identified in the novel identification methods.

In a particular embodiment, the invention provides a method of prophylaxis or treatment of dys-adaptive syndromes such as an animal or human pain syndrome. A pain syndrome can manifest for a variety of reasons - some local, such as, for example, as the result of enthesitis or inflammatory arthropathy, and some referred, such as, for example, as the result of nerve root compression, disk herniation and/or sciatica.

The invention will be described hereinafter with reference to these applications. However, it will be appreciated that the invention is not limited to this particular field of use.

BACKGROUND OF THE INVENTION

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 the common general knowledge in the field.

Methods for the identification of a target area for delivery of a therapeutic operant include the determination of a site of anatomical deficiency by sectional anatomical imaging techniques such as anatomical X-ray imaging, ultrasound (US), Magnetic Resonance Imaging (MRI) or computed tomography (CT) and functional Magnetic Resonance Spectroscopy (MRS), Magnetic Resonance Spectroscopic Imaging (MRSI), Optical Coherence Tomography (OCT), Electron magnetic resonance (EMR), Synchrotron tomography, Symplectic Phase-Space Tomography (Palpography), Positron emission tomography (PET) or Single photon emission computed tomography (SPECT) or Magnetoencephalography (MEG).
Similarly, the above-mentioned anatomical imaging techniques have been employed in combination with molecular bone scans to identify abnormalities and sites of deficiencies or excess in bone. Molecular scans generally utilise radiopharmaceuticals comprising radioisotopes linked to tissue and/or process specific tracers such that the site of incorporation or metabolism of the tracer can be detected. A bone scan, for example, generally detects the uptake and covalent binding of radioisotopes linked to phosphonate tracers, such as hydroxymefhane diphosphonate (HDP) or methylene diphosphonate (MDP), into calcium sequestering substrates in the mineralising matrix of bone. This uptake is widely recognised to be the result of osteoblastic activity and, accordingly, is exclusively used to analyse bone.

The combinatorial scanning of a subject with different scanning modalities (e.g. anatomical X-ray, US, CT, MRI and functional MRS, MRSI, OCT, EMR, Synchrotron tomography, PET, ion cyclotron resonance (ICR), independent component analysis (ICA), MEG, bone scan, joint scan, SPECT scan, or palpography requires that the acquired data/signal be registered onto the same coordinate system. Co-registration of the signals detected from a multi-modality scan allows comparison and/or integration of signals obtained from the different measurements in order to produce a co-registered image for clinical evaluation, and ultimately for the identification of anatomical deficiencies.

In cases where anatomical imaging alone or in combination with molecular scans allows the identification of an anatomical deficiency believed to be the cause of pain experienced by the subject, administration of analgesic drugs may be directly targeted to the specific site of deficiency. However, such anatomical deficiencies are not always painful. For example, anatomical deficiencies such as nerve compressions are often diagnosed during ancillary examinations of completely pain free patients. It is increasingly appreciated that macro and micro environmental ischemia, trauma, instability, inflammation, congestion and/or oedema at a site of deficiency (e.g. a site of nerve canal stenosis leading to nerve compression) can be the cause of the pain perceived by the patient.

Accordingly, common treatment regimes for pain syndromes attributed to nerve root compression, herniation and/or sciatica include targeted administration (for example via injection) and non-targeted administration (for example via oral delivery) of analgesic and anti-inflammatory drugs such as steroidal and non-steroidal anti-inflammatory drugs.
In cases where these treatment regimes do not alleviate the patient's pain, specialist surgeons are often consulted in order to surgically correct the diagnosed anatomic deficiency held to be the underlying cause of the pain syndrome. Surgical intervention is generally the last resort for the long-suffering patient and, as such, typically follows extended periods of conservative pain management including rest, traction and drug therapy. Unfortunately, a significant proportion of these patients do not get permanent or significant or sufficient pain relief (presumably due to mis-targeting, misdiagnosis and/or misplacement) resulting in failed joint replacement syndrome or failed back syndrome for instance.

As indicated above, anatomical deficiencies are generally visualised by anatomical imaging and the images are assessed to supplement the clinical diagnosis. On the basis of anatomical images, it is deduced or inferred whether the pain perceived by the patient can be attributed to an anatomical deficiency near the region of perceived pain rather than potentially being the result of another anatomical deficiency remote from this region. For example, pain perceived in the hip region may be the result of an anatomically deficient hip joint but may also be caused by an anatomical deficiency of the patient's back or knee, labrum, bursa, cuff, tendon, enthesis, pelvis, sacroiliac joint, spine or brain. Anatomical imaging is often repeated prior to surgical intervention in order to evaluate for possible interval anatomic evolution and to confirm a previous diagnosis thereby necessarily adding to the total cost of long-lasting treatment.

Counter-intuitively, though considered a permanent treatment, most surgical treatments do not effect a permanent cure (presumably because the premise or cause underlying the dys-adaptive state is not able to be fully redressed by removing tissue or fusing one or more levels). This scenario comes under the group of conditions, which together are designated "failed back surgery syndrome". Very often anatomical imaging is completely normal for the postoperative state but the patient is left with recurrent or unremitting pain for which no cause can be detected on a standard imaging workup. Our findings show that this group of symptoms has a number of causal features which are particularly frustrating to the patient who "had a prolapse" or other anatomical deficiency, which was surgically corrected but where, for example, the back pain remains - despite an excellent surgical result. Depression ensues more frequently if there is no demonstrable cause for the pain and typically the sufferer is referred to a psychiatrist.

Recent advances in diagnostic molecular imaging technologies appear to have received little attention in the general field of treatment of pain syndromes. Most surgeons continue to prefer anatomic imaging to supplement a clinical diagnosis such that confirmation for surgical
intervention is generally still based on anatomical imaging. Only occasionally non-co-registered molecular imaging techniques such as positron emission tomography (PET) or single photon emission tomography (SPECT) scans are used to confirm clinical diagnosis prior to surgical intervention. This reflects the long-held belief in the community of medical practitioners treating pain syndromes that the major component of the perceived pain results from an anatomical bone deficiency such as compression or stenosis or an unstable or slipped joint of sorts which is best diagnosed clinically with the aid of certain anatomical images. Generally, the surgical interventions to redress these anatomical deficiencies include the removal of narrowing or offending tissue or the fusion of unstable joints. The problem of relying on surgery alone has lead to the valuable contribution of professional physiotherapy and targeted or graded physical therapy as a means to re-establish function and reduce the dys-adaptive responses which often (almost invariably) underlie prolongation of pain, chronic pain and failure or reduced success of the total intervention from conservative medical management, surgery, physiotherapy, occupational therapy, rehabilitation and workforce retraining schemes. It is estimated that this cost the Australian population of 17.5 million people, in excess of 31 billion dollars in 2007 alone.

Although anatomical deficiencies such as sites of compression of nerves and/or nerve roots are generally considered anatomical deficiencies causative in the diagnosis of acute pain syndromes, the present invention relates to the finding that an initial insult and resultant deficiency may heal completely and be of only partial or entirely incidental import to the maintenance of subacute or more chronic pain syndromes. It has been found that large and narrowed facets in the cervical, thoracic, lumbar and sacral spine may be completely asymptomatic despite the presence of subacute or chronic stenosis and inferred compression of nerves and/or nerve roots. On the other hand, non-compressive inflammation, ischemia, congestion or instabilities of nerves and/or nerve roots or their membranes (neuritis, peri-neuritis or arachnoiditis, respectively) are 1) observable and 2) are commonly found to generate symptoms in patients presenting with subacute and chronic pain dys-adaptive or painful syndromes and 3) may be traced through the tiers of insufficiently adaptive responses as primary, secondary, tertiary, quaternary phenomena which, if addressed With targeted therapeutics, result in pain amelioration.

Similarly narrowed (degenerate) joints and large (hypertrophic) joints are not necessarily painful. Similarly, in the extreme situation of "bone-on-bone" arthrosis, which can readily be imaged by anatomical imaging techniques, is found not to be necessarily painful (unless also
inflamed). Hence, an orthopaedic surgeon relying solely on anatomical images showing for example a mildly, moderately or even severely narrowed hip joint to assert the clinical diagnosis may inadvertently replace the patient's hip joint despite the fact that it is not the primary or only cause of the patient's hip region pain. Regrettably, though becoming less common, we have documented many cases of prosthetic replacement of a perfectly serviceable joint, which have been retrospectively proven as irrelevant to the causal rank of the patient's prosthetic placement region pain. This was particularly common in patients where a prosthetic replacement of the hip was performed but where a back amas was referring to the hip, leaving the patient with remaining pain after hip replacement (but also with the foreign material of, for example a cobalt metallic prosthesis and all its accompanying costs, risks and detriment to the individual. The unfortunate pain sufferer is often left without a diagnosis for their pain and the likelihood that the prosthetic placement will eventually loosen, requiring regular revision and increasing the risk of potential infection and the most disastrous outcome of subsequent disarticulation.

Therefore it is clear that there is a requirement for new methods of prophylaxis and treatment of pain syndromes, which allow more effective identification, treatment and palliation of the underlying causes of the syndromes thereby avoiding inefficient, high-cost, extended treatment regimes with expensive and often dependence- or resistance-inducing drugs.

Known methods of treating tumours and in particular cancerous tumours include surgery, radiotherapy and the administration of therapeutic operants such as: chemotherapeutic drugs, immunotherapeutic drugs, hormones, or drugs containing small molecules for targeted therapy which generally inhibit enzymatic domains on mutated, over-expressed, or otherwise critical proteins within the cancer cells. However, the administration of therapeutic operants used in the treatment of tumours is generally a systemic delivery via the subject's blood stream. Systemic delivery necessarily exposes not only the tumour tissue to the effects of the administered operants. While many of the drugs being administered in the treatment of cancerous tumours have therapeutic use for the subject being treated due to their effect on the cancerous tumour cells, their overall effects on non-cancerous cells are often detrimental leading to severe physiological and psychological suffering of the subject being treated.

Therefore it is clear that there is a requirement for new methods of treating a tumour, which allow direct injection of a therapeutic operant into a cancerous tumour, thereby avoiding
detrimental effects of the operant on non-cancerous cells leading to severe physiological and psychological suffering of the subject being treated.

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.

**SUMMARY OF THE INVENTION**

It has been surprisingly found that a target area for delivery of a prophylactic or therapeutic operant can be identified in a sectional image obtained by anatomical imaging techniques such as X-ray, X-ray computed tomography (CT), sectional imaging ultrasound and Magnetic Resonance Imaging (MRI).

Further, this target area can be identified in a co-registered image obtained by the combinatorial use of one of the above-mentioned imaging techniques with a molecular scan such as Magnetic Resonance Spectroscopy (MRS), Magnetic Resonance Spectroscopic Imaging (MRSI), Electron magnetic resonance (EMR), ion cyclotron resonance (ICR), independent component analysis (ICA), Synchrotron tomography, a bone scan, a Positron Emission Tomography (PET) scan or Magneitoencephalography (MEG).

In some preferred embodiments this identification provides the basis for new methods of prophylaxis or treatment of a disease or treatment of trauma in a patient wherein the operant may be delivered to the target area. An additional benefit of the methods of the present invention is that the patient is generally exposed to significantly less radiation as the methods require less radiopharmaceutical to be administered.

In a first aspect the present invention relates to a method of identifying a target area for the delivery of a prophylactic or therapeutic operant, wherein said target area is in tissue which is substantially not bone tissue, said method including the steps of:

(a) Scanning a subject, or one or more portions of said subject, using anatomical imaging selected from X-ray computed tomography (CT), sectional imaging ultrasound and Magnetic Resonance Imaging (MRI) in combination with a signal from a molecular bone scan to obtain a co-registered image of said subject or said one or more portions of said subject; and
(b) Truncating the signal of said molecular bone scan in said co-registered image such that visibility of said signal in said image is enhanced in the target area.

In a second aspect the present invention relates to a method of identifying a target area for the delivery of a prophylactic or therapeutic operant in an image of a subject, or of one or more portions of said subject, wherein said image is obtained by scanning said subject, or one or more portions of said subject, using anatomical imaging selected from X-ray, X-ray computed tomography (CT), sectional imaging ultrasound and Magnetic Resonance Imaging (MRI), and wherein said target area is determined by a loss of clarity/contrast of a soft-tissue plane. This loss of contrast may be visible due to bulk water reducing the frequency gradient across this plane and may include, for example, a smudge or blurring loss of clarity of a subjacent or surrounding boundary to a plane.

Preferably the anatomical imaging is X-ray CT and wherein the molecular bone scan is a Single Photon Emission Computed Tomography (SPECT) scan detecting radiation emitted from a radiopharmaceutical. The SPECT scan preferably detects gamma radiation emitted from a radiopharmaceutical comprising technetium-99m (99mTc)-phosphonate/phosphate. Preferably the (99mTc)-phosphonate/phosphate is selected from hydroxymethylene diphosphonate (HDP) and methylene hydroxyl diphosphonate (MDP).

Typically, the radiopharmaceutical is administered to the subject prior to the scanning at a dosage ranging from about 50 MBq to about 1200 MBq. The dosage preferably ranges from about 50 MBq to about 500 MBq. The skilled addressee will understand that the radiopharmaceutical can also be administered at a dosage ranging from about 50 MBq to about 1100 MBq, from about 50 MBq to about 1000 MBq, from about 50 MBq to about 900 MBq, from about 50 MBq to about 850 MBq, from about 50 MBq to about 800 MBq, from about 50 MBq to about 750 MBq, from about 50 MBq to about 700 MBq, from about 50 MBq to about 650 MBq, from about 50 MBq to about 600 MBq, from about 50 MBq to about 550 MBq, from about 50 MBq to about 500 MBq, from about 50 MBq to about 450 MBq, from about 50 MBq to about 400 MBq, from about 50 MBq to about 350 MBq, from about 50 MBq to about 300 MBq, from about 50 MBq to about 250 MBq, from about 50 MBq to about 200 MBq, from about 50 MBq to about 150 MBq, from about 50 MBq to about 100 MBq, from about 100 MBq to about 1100 MBq, from about 150 MBq to about 1000 MBq, from about 200 MBq to about 900 MBq, from about 250 MBq to about 850 MBq, from about 300 MBq to about
800 MBq, from about 350 MBq to about 750 MBq, from about 350 MBq to about 700 MBq,
from about 350 MBq to about 650 MBq, from about 350 MBq to about 600 MBq, from about
350 MBq to about 550 MBq, from about 350 MBq to about 500 MBq or from about 350 MBq to
about 450 MBq.

Preferably the target area is in tissue which is substantially in soft tissue. More preferably, the
target area in the soft tissue is substantially at the soft tissue - bone tissue boundary.

In a third aspect the present invention relates to a method of prophylaxis or treatment of pain or
disease or a method of treatment of trauma, said method including the steps of identifying a
target area according to the first aspect and delivering a therapeutically effective amount of an
operant to said target area.

Preferably the target area is substantially remote from a site of pain, disease or trauma.

Preferably the pain is caused by a pain syndrome. Generally the pain syndrome is selected from
the group consisting of complex pain syndrome; chronic pain syndrome; regional pain
syndrome; relapsing pain syndrome; loco-regional pain syndrome; acute or chronic pain
syndrome; amorphous pain syndrome; deep pain syndrome; recurrent pain syndrome; remitting
pain syndrome; resistant pain syndrome; shooting pain syndrome; sharp pain syndrome; electric
pain syndrome; evanescent pain syndrome; benign pain syndrome; malignant pain syndrome;
parenchymal pain syndrome; integumentary pain syndrome; occult or otherwise hidden or
obtuse pain syndrome; forensic pain syndrome; complex regional pain syndrome;
compensational pain syndrome; prosthetic pain syndrome; peri-prosthetic; pain syndrome
referred pain syndrome; atypical pain syndrome; post-surgical pain and phantom pain syndrome.

Typically the pain syndrome is caused by nerve root compression, disk herniation and/or
sciatica.

Further, the disease typically causes inflammation. In one or more preferred embodiments the
inflammation is periarthritis, tendonopathy, peritenonitis, neuritis, enthesitis, symphysitis,
myositis, myotendonitis, pericarditis, mesothelial inflammation, serositis, adventitial
inflammation, periarteritis, or arteritis.
The step of delivering a therapeutically effective amount of said operant to the target area preferably counters secretion or effects of cytokines, chemotactic cytokines or chemokines such as interleukins and tumour necrosis factors.

In one or more preferred embodiments the disease is caused by an orthodox treatment-resistant infection. In some preferred embodiments the orthodox treatment-resistant infection is a Methicillin-resistant Staphylococcus aureus (MRSA) infection.

Generally the operant is ozone and the therapeutically effective amount of the ozone ranges from about 10 ml to about 100 ml of ozone at a concentration ranging from about 0.01 µg/ml to about 1000 µg/ml. Preferably the therapeutically effective amount ranges from 10 ml to about 40 ml of ozone at a concentration ranging from: about 1 µg/ml to about 40 µg/ml, preferably 25 µg/ml, for the treatment of pain; about 1 µg/ml to about 60 µg/ml, preferably 30 µg/ml, for the treatment of inflammation; about 20 µg/ml to about 120 µg/ml, preferably 90 µg/ml, for the treatment of tumours; about 1 µg/ml to about 25 µg/ml, preferably 15 µg/ml, for the treatment of ischemia; about 1 µg/ml to about 25 µg/ml, preferably from about 5 µg/ml to 15 µg/ml, to effect beneficial immune-modulation and/or immune adaptation; or about 1 µg/ml to about 25 µg/ml, preferably 5 µg/ml, to effect enhanced graft take.

The skilled addressee will understand that ozone can be also be administered at a concentration ranging from about 0.1 µg/ml to about 900 µg/ml, from about 0.2 µg/ml to about 800 µg/ml, from about 0.3 µg/ml to about 700 µg/ml, from about 0.4 µg/ml to about 600 µg/ml, from about 0.5 µg/ml to about 500 µg/ml, from about 0.6 µg/ml to about 400 µg/ml, from about 0.7 µg/ml to about 300 µg/ml, from about 0.8 µg/ml to about 200 µg/ml, from about 0.9 µg/ml to about 150 µg/ml, from about 1 µg/ml to about 120 µg/ml, from about 1 µg/ml to about 110 µg/ml, from about 1 µg/ml to about 100 µg/ml, from about 1 µg/ml to about 90 µg/ml, from about 1 µg/ml to about 80 µg/ml, from about 1 µg/ml to about 70 µg/ml, from about 1 µg/ml to about 60 µg/ml, from about 1 µg/ml to about 50 µg/ml, from about 1 µg/ml to about 45 µg/ml, from about 1 µg/ml to about 35 µg/ml, from about 1 µg/ml to about 30 µg/ml, from about 1 µg/ml to about 25 µg/ml, from about 1 µg/ml to about 20 µg/ml, from about 1 µg/ml to about 15 µg/ml, from about 1 µg/ml to about 10 µg/ml, from about 5 µg/ml to about 120 µg/ml, from

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about 10 µg/ml to about 120 µg/ml, from about 15 µg/ml to about 20 µg/ml, from about 25 µg/ml to about 120 µg/ml, from about 30 µg/ml to about 120 µg/ml, from about 35 µg/ml to about 120 µg/ml, from about 40 µg/ml to about 120 µg/ml, from about 45 µg/ml to about 120 µg/ml, from about 50 µg/ml to about 120 µg/ml.

5 from about 55 µg/ml to about 120 µg/ml, from about 60 µg/ml to about 120 µg/ml, from about 65 µg/ml to about 120 µg/ml, from about 70 µg/ml to about 120 µg/ml, from about 75 µg/ml to about 120 µg/ml, from about 80 µg/ml to about 120 µg/ml, from about 85 µg/ml to about 120 µg/ml, from about 90 µg/ml to about 120 µg/ml, from about 95 µg/ml to about 120 µg/ml, from about 100 µg/ml to about 120 µg/ml, from about 105 µg/ml to about 120 µg/ml, from about 110 µg/ml to about 120 µg/ml or from about 115 µg/ml to about 120 µg/ml.

The skilled addressee will also understand that the ozone can also be administered at a volume from about 10 ml to about 95 ml, from about 10 ml to about 90 ml, from about 10 ml to about 85 ml, from about 10 ml to about 80 ml, from about 10 ml to about 75 ml, from about 10 ml to about 70 ml, from about 10 ml to about 65 ml, from about 10 ml to about 60 ml, from about 10 ml to about 55 ml, from about 10 ml to about 50 ml, from about 10 ml to about 45 ml, from about 10 ml to about 40 ml, from about 10 ml to about 35 ml, from about 10 ml to about 30 ml, from about 10 ml to about 25 ml, from about 10 ml to about 20 ml, from about 10 ml to about 15 ml, from about 15 ml to about 100 ml, from about 20 ml to about 100 ml, from about 25 ml to about 100 ml, from about 30 ml to about 100 ml, from about 35 ml to about 100 ml, from about 40 ml to about 100 ml, from about 45 ml to about 100 ml, from about 50 ml to about 100 ml, from about 55 ml to about 100 ml, from about 60 ml to about 100 ml, from about 65 ml to about 100 ml, from about 70 ml to about 100 ml, from about 75 ml to about 100 ml, from about 80 ml to about 100 ml, from about 85 ml to about 100 ml, from about 90 ml to about 100 ml or from about 95 ml to about 100 ml.

Further, the skilled addressee will appreciate that the ozone can be administered as part of any treatment regime including but not limited to the treatment of pain, inflammation, tumours, ischemia or a treatment regime to effect beneficial immune-modulation and/or immune

adaptation or to effect enhanced graft take.

In some preferred embodiments the step of delivering a therapeutically effective amount of the operant to the target area includes inhaled delivery, ingested delivery, per cutaneous delivery, per rectal delivery, per mucosal delivery, per nasal delivery, per optic delivery, trans-cutaneous delivery,
delivery, trans-visceral delivery, trans-cranial delivery, trans-mucosal delivery, pleothermal delivery, hyperbaric delivery, isobaric delivery or hypobaric delivery.

Preferably the step of delivering a therapeutically effective amount of the operant includes injection of the operant.

In a fourth aspect the present invention relates to a method of identifying a direct injection target area for direct injection of a therapeutic operant in an image of a subject or of one or more portions of said subject, wherein said image is obtained by scanning said subject, or one or more portions of said subject, using anatomical imaging selected from X-ray computed tomography (CT), sectional imaging ultrasound and Magnetic Resonance Imaging (MRI), and wherein said target area is determined by a loss of clarity/contrast of a soft-tissue plane. Again, the loss of clarity/contrast may include, for example, a smudge or blurring loss of clarity of a subjacent or surrounding boundary to a plane.

Preferably the direct injection target area is in tissue which is substantially not bone tissue, and the image is a co-registered image of the subject or the one or more portions of the subject obtained by scanning the subject, or the one or more portions of the subject, using anatomical imaging selected from X-ray computed tomography (CT), sectional imaging ultra sound and Magnetic Resonance Imaging (MRI) in combination with a signal from a Positron Emission Tomography (PET) scan, and wherein the target area is further determined by truncating the signal of the PET scan in the co-registered image such that visibility of the signal in the image is enhanced in the target area.

Preferably the anatomical imaging is X-ray CT and wherein the PET scan detects radiation emitted from a radiopharmaceutical. The PET scan preferably detects positrons emitted from a radiopharmaceutical comprising fluorine-18 (18F-PET) fluorodeoxyglucose (FDG-PET).

In a fifth aspect the present invention relates to a method of treating a tumour comprising administration of a therapeutic operant to a direct injection target area identified according to any one of the methods according to the fourth aspect.

Typically the tumour is a cancerous tumour. Preferably the administration is direct injection into said target area. The therapeutic operant preferably is ozone.
Generally the therapeutically effective amount of the ozone ranges from about 10 ml to about 100 ml of ozone at a concentration ranging from about 20 \(\mu\)g/ml to about 120 \(\mu\)g/ml, preferably 90 \(\mu\)g/ml.

Any and all values within these ranges will also be used in certain embodiments of the invention.

In a sixth aspect the present invention relates to a method of treating a dysadaptive or dysfunctional illness comprising administration of a therapeutic operant to a direct injection target area identified according to the fourth aspect.

Preferably, the dysadaptive or dysfunctional illness is caused by toxicity, metabolic imbalance, trauma such as a burn, ischemia, hyper immunity, autoimmunity, innate immunity, transplant rejection, adaptive immunity, infection, inflammation, degeneration, incomplete regeneration, incomplete hybrid vigour or incomplete wellness.

**DEFINITIONS**

In the context of this specification the following terms are defined as follows:

"amas" (aggregated inicro-cluster anotnaly state)

This may be an area visible in an image obtained by scanning a subject, or one or more portions of said subject, using anatomical imaging selected from X-ray, X-ray computed tomography (CT), sectional imaging ultrasound and Magnetic Resonance Imaging (MRI) as a loss of clarity/contrast of a soft-tissue plane. Without wishing to be bound by theory, this loss of clarity may be visible due to bulk water reducing the phase coherent frequency gradient across this plane and may include, for example, a smudge or blurring loss of clarity of a subjacent or surrounding boundary to a plane.

It may also be an area identified in a co-registered image obtained by scanning a subject, or one or more portions of the subject, using anatomical imaging selected from X-ray computed tomography (CT), sectional imaging ultrasound and Magnetic Resonance Imaging (MRI) in combination with a molecular bone scan, by truncating the signal of the molecular bone scan in...
the co-registered image such that visibility of the signal of the molecular bone scan in the image is enhanced in tissue which is substantially not bone tissue.

The amas appears to be the dys-adaptive biomechanical, neural and/or anatomico-pathologic correlate for the conscious pain syndrome. It is identified by protocols herein described using standard imaging techniques. Previously, an amas was not perceived on such images (it should be noted that perception has been made much easier by new and state-of-the-art imaging technologies, which, like all direct digital or high end technologies, improves the conspicuity of these otherwise subtle findings). Moreover, the significance is that these areas may be identified to rectify dysadaptive phenomena or chronic dysfunction, illness or pain syndromes.

The commonality of this amas identification across many different pathologies (biomechanical, burns, toxic, trauma, tumour, infective, ischemic, inflammatory, immune, congestive etc) indicates that a targeted management is appropriate.

Please note that throughout the specification, the terms "amas" and "target area" are used interchangeably.

"truncation"

In the context of the specification, the term "truncation" refers to the manipulation of a signal within a co-registered image to provide enhanced visibility of the signal in a target area within the field of view.

"comprising"

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".

"bone tissue"

Bone tissue is a specialized form of connective tissue and is the main element of the skeletal tissues. It is composed of cells and an extracellular matrix in which fibres are embedded. Bone tissue is unlike other connective tissues in that the extracellular matrix becomes calcified.
"soft tissue"
In contrast to bone tissue as defined above, "soft tissue" refers to tissues that connect, support, or surround other structures and organs of the body but do not become calcified. Soft tissue includes tendons, ligaments, fascia, fibrous tissues, fat and synovial membranes, muscles, nerves and blood vessels.

"soft tissue-bone tissue boundary"
The "soft tissue-bone tissue boundary" is the area between bone tissue and soft tissue.

"substantially remote"
In so far as this term relates to a target area, the term means that the target area is not directly at the site of anatomical deficiency.

"operant"
An "operant" is a physical prophylactic or therapeutic agent which may be utilised in conjunction with a carrier (meaning a mixture, admixture or entrainment) including, but not limited to, steroidal anti-inflammatories, non-steroidal anti-inflammatories.

Operants typically have certain physical commonalities of delocalized electron or pi-field, Debye/London force or ordered water or dipole resonances or quantum electro dynamical moiety (often electro-negative on proteins and sugars, lipoproteins or lipo-glyco-proteins).

Operants may be:
- hydrated titrations of elemental and molecular water dilutions, organic bio-tissues of protein, sugar or fat constituents or inorganic elemental or molecular oxides such as ozone, H₂O, H₂O₂, NO, HC₅N, CO, SO₂, SH₂ or carboxides;
- simple and polymeric sugars of dextrose, fructose, glucose and polyethylene glycol, including relevant alcohols;
- simple or polymeric fatty moieties or glycoproteins such as aromaticoils, isoprenes, monoterpenols, sesquiterpenols, phenols, aldehydes, ketones, acids, esters, ethers, oxides, lactones, coumarins, monoterpenes and sesquiterpenes;
- fats such as polyunsaturated oils, olifins and unconjugated aliphatics; or
simple or polymeric organic bio-tissues of protein, sugar or fat constituents including placental cord isolates and fetal tissue or stem cell isolates, proteinaceous compounds such as amino acid mixtures, plasma or serum components.

The preferred operant in the context of the present invention is ozone.

"CCTV-MI" - Co-registered Computed Tomography Validated Molecular Imaging

In the context of the present invention, CCTV-MI refers to the combinatorial use of different scanning modalities such as anatomical X-ray, US, CT, MRI and functional/molecular imaging techniques such as MRS, OCT, PET, bone scan, joint scan, SPECT scan, or palpography.

BRIEF DESCRIPTION OF THE DRAWINGS

A preferred embodiment of the invention will now be described, by way of example only, with reference to the accompanying drawings in which:

Figures 1.1- 1.9 are series of CCTV-MI images showing a target area for the delivery of an operant in a method of treatment of thoracic inflammatory arthropathy according to a preferred embodiment of the invention;

Figure 2.1 is a series of CCTV-MI images showing a target area for the delivery of an operant in a method of treatment of right shoulder pain resulting from a pathological fracture of the right clavicle according to a preferred embodiment of the invention;

Figure 3.1 contains sagittal X-ray images showing a target area for the delivery of an operant in a method of treatment of left distal fibular pain resulting from a sub-threshold left tibia stress fracture defined by a loss of clarity of myofascial fat planes according to a preferred embodiment of the invention;

Figures 3.2 and 3.3 are series of CCTV-MI images showing a target area for the delivery of an operant in a method of treatment of left distal fibular pain resulting from a sub-threshold left tibia stress fracture according to a preferred embodiment of the invention;

Figures 4.1 and 4.2 are series of CCTV-MI images showing a target area for the delivery of an operant in a method of chronic back pain syndrome according to a preferred embodiment of the invention;
Figures 5.1 and 5.2 are series of CCTV-MI images showing target areas for the delivery of an operant in a method of treatment of lower back pain according to a preferred embodiment of the invention, the target areas being illustrated at the dorsal rami of lumbar vertebra L4 and L5 and spanning several thoracic vertebra;

Figures 5A.1 and 5A.2 are series of CCTV-MI images showing target areas for the delivery of an operant in a method of treatment of shoulder and neck pain caused by thoracic spondylitis, the target areas being identified at thoracic vertebra T1, T3 - T5 and b and less pronounced at T8;

Figure 6.1 and 6.2 are series of CCTV-MI images showing a target area for the delivery of an operant in a method of treatment of left ankle and big toe pain with intermittent infection according to a preferred embodiment of the invention, illustrating one target area at the base of the proximal phalanx of the foot and two bilateral target areas at the subtalar compartment;

Figures 6.3 and 6.4 show the target areas of the left foot shown in Figures 6.1 and 6.2 in series of lateral CCTV-MI images;

Figure 7.1 to 7.3 are series of transverse CCTV-MI images showing bilateral target areas at the sacroiliac joints for the delivery of an operant in a method of treatment of lower back pain according to a preferred embodiment of the invention;

Figures 7.4 and 7.5 are series of sagittal CCTV-MI images showing bilateral target areas for the delivery of an operant in a method of treatment of lower back pain according to a preferred embodiment of the invention at the L5 nerve roots;

Figure 7.6 is a series of sagittal CCTV-MI images showing a target area for the delivery of an operant in a method of treatment of lower back pain according to a preferred embodiment of the invention indicative of right hip sinovitis;

Figures 8.1 to 8.10 are a series of X-ray CT images showing target areas for the delivery of an operant in a method of treatment of diffuse abdominal pain in a patient according to a preferred embodiment of the invention;
Figure 9.1 is a series of X-ray CT images showing target areas for the delivery of an operant in a method of treatment of general abdominal pain in a patient according to a preferred embodiment of the invention;

Figure 9.2 is an inversion of the image series shown in Figure 9.1;

Figure 10.1 is a series of X-ray CT images showing target areas (uterine amas indicative of endometriosis) for the delivery of an operant in a method of treatment of general pelvic pain in a patient according to a preferred embodiment of the invention;

Figure 10.2 is an inversion of the image series shown in Figure 10.1;

Figure 11.1 is a series of X-ray CT images showing target areas (terminal ileum amas) for the delivery of an operant in a method of treatment of general abdominal pain and bloating in a patient according to a preferred embodiment of the invention;

Figure 11.2 is an inversion of the image series shown in Figure 10.1;

Figures 12.1 to 12.8 are series of X-ray CT images showing a target area (tumour of the ascending colon) for the delivery of an operant in a method of treatment of radiating abdominal pain in a patient according to a preferred embodiment of the invention;

Figures 13.1 to 13.7 are series of CCTV-MI images showing target areas for the delivery of an operant in a method of treatment of bilateral thigh and pelvic MRSA infection in a patient according to a preferred embodiment of the invention; and

Figure 14.1 is a graph showing the reduction in tumour size (in mm) in response to direct ozone injection into a target area for the delivery of an operant according to a preferred embodiment of the invention.

**PREFERRED EMBODIMENT OF THE INVENTION**

Generally, in a method of treating pain according to one or more preferred embodiments of the present invention, patients, on average, experience significant relief from the pain after approximately 4 treatments.
In a treatment of acute pain according to one or more preferred embodiments of the present invention, the operant is typically delivered up to twice per week such that the treatment period generally ranges from about 2 to about 4 weeks for patients presenting with acute pain.

In a treatment of acute pain according to one or more preferred embodiments of the present invention, the operant is typically delivered once every 1 to 2 weeks such that the treatment period generally ranges from about 4 to about 8 weeks.

A preferred embodiment of the invention will now be described, by way of example only, with reference to the examples.

Example 1
Patient presented with a two year history of neck pain (right > left), radiating into both shoulders posterior and pins and needles in all fingers. Patient injured her shoulder twice while doing repetitious heavy lifting. No history of sinister or malignant disease.

Diagnostic imaging by co-registered computer tomography validated molecular imaging (CCTV-MI) was performed and assessment of the obtained images showed typical thoracic inflammatory arthropathy as highlighted in figures 1.1 and 1.9. Figures 1.2 to 1.8 show that all itemised levels would appear as normal on CT images. By way of visualizing, the target area for the delivery of the operant was identified at T1, T2, T4, T5, T7, T9 and T11.

Age: 54 years old
Gender: Female
Type and dosage of radiopharmaceutical administered during imaging 300 MBq of (⁹⁹m Tc)-HDP
Anatomical location: T1, T2, T4, T5, T7, T9, T11
Sites of delivery of operant: T1, T2, T4, T5, T7, and T9 bilaterally
Diagnosis: Thoracic inflammatory arthropathy
Treatment: Percutaneous therapy of thoracic region as indicated bilaterally.
Target area remote: Yes, cervical spine pain. The thoracic spine was the cause of the cervical spine pain.

Operant and dosage used: total of 30ml ozone at [30 µg/mL] per treatment
Number of treatments: 3
Number of needles at each treatment: 6
Other medications: Nil
Clinical overview: Radiating cervical pain that reaches the fingers in the right arm. Appearances are fairly typical of thoracic inflammatory arthropathy, perhaps explaining the upper dorsal limb symptom complex and neck pain. There is no high grade inflammation in the cervical spine.

Clinical outcome: The pain scale score before treatment was 7 and after treatment was recorded as being 3. The pain was resolved, inhibition of activity of daily life had renormalised.

Example 2
Cancer patient presented with right shoulder pain for investigation.

Diagnostic imaging by co-registered computer tomography validated molecular imaging (CCTV) was performed and assessment of the obtained images showed clearly an AMAS fracture through the mid shaft right clavicle which is an essentially "cold" central focus with post traumatic periosteal activity as highlighted in figure 2.1.

Age: 50 years old
Gender: Female
Type and dosage of radiopharmaceutical administered during imaging: 500 MBq of ($^{99m}$Tc)-HDP
Anatomical location: Right clavicle
Sites of delivery of operant: Right clavicle amas
Diagnosis: Pathological fracture of right clavicle
Treatment: Percutaneous therapy of right clavicle before and after cancer-related radiotherapy for pain relief and bone healing benefit and to reduce the likelihood of osteonecrosis and skin inflammation, which is a side effect of radiotherapy.
Target area remote: Yes, radiating throughout shoulder region
Operant and dosage used: total of 15ml ozone at [30µg/ml] per treatment
Number of treatments: 3
Number of needles: 6
Other medications: Narcotics for pain management

Clinical overview: Clear evidence of a pathologic fracture in the right clavicle. No other metastatic disease within the bone. There is a left adrenal lesion and some lymph node prominence better seen of the recent standard protocol CT.

Clinical outcome: The patient recorded a score of 9 on the pain scale before treatment and a score of 5 at the conclusion of treatment. The patient required no further narcotics for pain management and had
some substantial bony healing. Patient experienced marked improvement in the quality of daily life, despite metastatic bone disease.

**Example 3**

Patient presented with a two week history of left distal fibula pain. No history of sinister or malignant disease.

Diagnostic imaging by co-registered computer tomography validated molecular imaging (CCTV-tvlII) was performed and assessment of the obtained images showed the fibular has a sub-threshold injury as highlighted in Figure 3.1. Figure 3.2 is an inversion of Figure 3.1 further illustrating the amas identified in Figure 3.1.

Age: 17 years old  
Gender Female  
Type and dosage of radiopharmaceutical administered during imaging: $500 \text{MBq of } (^{99m}\text{Tc})\text{-HDP}$  
Anatomical location: left tibia  
Sites of delivery of operant: tibia, mid-shaft injected  
Diagnosis: Sub-threshold left tibia stress fracture / insufficiency of bone strength  
Treatment: Percutaneous therapy of identified regions of activity and crutches  
Target area remote: Yes, radiating lateral pain i.e. poorly localized pain in the general area.

Operant and dosage used: total of 15ml ozone at [30μg/ml] per treatment  
Number of treatments: 3  
Number of needles: 6  
Other medications: Unknown

Clinical overview: There is a grade II/III stress fracture involving the lateral fibular shaft overlying high grade anterior and antcro-lateral periostitis with adjacent soft tissue swelling typical of an evolving bony injury (incomplete cortical infarction).

Clinical outcome: Complete healing and absence of pain. As an elite athlete the patient was able to have an early re-institution to cross-training.

**Example 4**

Patient presented with six-month history of chronic back pain, radiating across lower back laterally (left = right). Pain radiating down both legs posterior to the knees (right > left). Patient has known arthritis in the lumbar region. No history of sinister or malignant disease.
Diagnostic imaging by co-registered computer tomography validated molecular imaging (CCTV-MI) was performed and assessment of the obtained images showed extreme activity at L3/4 and L4/5 (dorsal elements, right lightly > left) which is proximate to exiting L3, transiting L4 nerve roots (bilaterally right > left). The exiting L5 on the right is probably also involved as highlighted in figures 4.1 and 4.2. By way of visualizing, the target area for the delivery of the operant was identified at L4/5 and L3/4 facets as well as the exiting L3 and L4 and transiting L4 and L5 nerve roots (bilaterally right = left).

Age: 45 years old

Gender: Female

Type and dosage of radiopharmaceutical administered during imaging: 500 MBq of (99mTc)-HDP

Anatomical location: L3/L4, L4/L5

Sites of delivery of operant: Exiting L3/L4 and L4/L5 nerve roots and facet joints

Diagnosis: Exiting L3/L4 and L4/L5 nerve roots and facet joints - patient evidenced chronic back pain syndrome with no CT, MRI or US evidence of abnormality. (US could not have penetrated this area well enough to have diagnostic value)

Treatment: Percutaneous therapy

Target area remote: Yes, radiating across entire lower back

Operant and dosage used: total of 30ml ozone at [30 µg/ml] per treatment

Number of treatments: 3

Number of needles: 8

Odier medications: Paracetamol for pain management

Clinical overview: There is extreme activity at L3/4 and L4/5 dorsal elements right slightly > than left which is proximate to L3, transiting L4 nerve roots (bilaterally, right > left). The exiting L5 on the right is probably also involved.

Clinical outcome: The patient recorded a 7 on the pain scale prior to treatment and recorded a 2 on the pain scale post-treatment. Complete resolution of radicular/locoregional pain syndrome.

Example 5

Patient presented with a ten-year history of intermittent lower back pain (left side only, around lumbar vertebra L5). No history of sinister or malignant disease.

Diagnostic imaging by co-registered computer tomography validated molecular imaging (CCTV-MI) was performed and assessment of the obtained images showed moderate accumulation in the lumbosacral junction as highlighted in figures 5.1 and 5.2. By way of
visualizing, the target area for the delivery of the operant was identified at the lower lumbar spine and both sacroiliac joints moving to the L4/5 facet and thoracic facets.

Age: 62 years old
Gender: Male

Type and dosage of radiopharmaceutical administered during imaging: 600 MBq of (\(^{99m}\)TcJ-HDP
Anatomical location: Lower back
Sites of delivery of operant: Both the lower lumbar spine and both sacroiliac joints and then subsequently, the L4/S facet and thoracic facets were injected

Diagnosis: Lower back pain
  1. Dorsal ramus irritation right L4 and Left L5 neuritis
  2. Thoracic amas presenting as lumbar-sacral pain syndrome

Treatment: Percutaneous therapy
Target area remote; Yes, radiating pain

  1. Thoracic amas
  2. Dorsal rami and transiting trunks right L4 nerve and left L5 nerve

Operant and dosage used: total of 30ml ozone at [30\(\mu\)g/ml] per treatment

Number of treatments: 3
Number of needles: 6

Other medications: Narcotic patches

Clinical overview: High grade accumulation in relation to the lumbosacral facet shows moderate activity in relation to the dorsal ramus in addition. There is minimal accumulation on the right side of L4/5 in a similar distribution (likely subclinical). Modest costotransverse arthritis at T7, T8 and T9 is incidental and probably secondary. Previous pain investigations including MRI stated "no compression" or "no abnormality seen".

Clinical outcome: The patient reported a pain score of 8 on the pain scale prior to treatment and over the pain chart series reduced to a pain scale of 4. The patient is virtually pain free, walking normally and is off narcotic patches for pain.

**Example 5A**
Patient presented with chronic right shoulder and neck pain. The patient had a nine-year history of cervical spine pain (right >left), radiating to the right shoulder superiorly to base of skull.

Intermittent numbness of right second phalanx/palmar aspect of the hand. No history of trauma, pain gradually worsening. No history of sinister or malignant disease.
Diagnostic imaging by co-registered computer tomography validated molecular imaging (CCTV-MI) was performed and assessment of the obtained images showed there is minimal accumulation in the cervical spine. However, moderate accumulation can be seen in relation to thoracic vertebrae T1, T3, T4, T5 and, to a lesser degree, T8. These changes appear bilateral (right slightly > left) as highlighted in figure 5a.2. Figure 5a.1 is an inversion of Figure 5a.2 further illustrating the changes identified in Figure 5a.2. By way of visualizing, the target area for the delivery of the operant was identified at the T1 exiting nerve root on the right and the capitus enthesis.

Age: 40 years old
Gender: Female
Type and dosage of radiopharmaceutical administered during imaging: 300 MBq of ($^{99m}$Tc-HDP
Anatomical location: Head and neck
Sites of delivery of operant: the cervical spine to hand pain - thoracic and right sternoclavicular (SC) joint amas were injected
Diagnosis: Thoracic spondylitis
Treatment: Percutaneous therapy for cervical, thoracic spine and hand
Target area remote: Yes, cervical spine to hand pain - thoracic and right sternoclavicular (SC) joint amas
Operant and dosage used: total of 30ml ozone at [30ug/ml] per treatment
Number of treatments: 3
Number of needles: 12
Other medications: Voltaren and narcotics for pain management

Clinical overview: There is moderate thoracic spine abnormality and mild capitus enthesitis bilaterally producing roto-torticollis in the cervical spine (secondary) - However, there appears to be no active accumulation within the cervical spine itself.

Clinical outcome: The patient reported a pain scale score of 9 prior to treatment and a pain scale of 4 and the conclusion of treatment. The patient has a complete resolution of symptoms and returned to an active lifestyle.

Example 6
Diagnostic imaging by co-registered computer tomography validated molecular imaging (CCTV-MI) was performed and assessment of the obtained images showed inflammatory arthropathy as highlighted in figures 6.1, 6.2, 6.3 and 6.4. By way of visualizing, the target area for the delivery of the operant was identified in the right mid and forefoot with inclusive treatment of the subtalar compartment and the talofibular aspects of the fusion.

Age: 50 years old
Gender: Male
Type and dosage of radiopharmaceutical administered during imaging: 800 MBq of (99mTc)-HDP (elevated dosage due primarily to peripheral vascular disease)
Anatomical location: Left foot
Sites of delivery of operant: Both feet were treated, specifically the talo-navicular (TN) articular insertion, the tibula anterior (TA) ligament, the fibular posterior (TP) ligament and the meta-tarso-phalageal (MTP) articulation.
Diagnosis: Intermittent infection and pain left foot symptoms - bilateral amas identified - may have to treat both feet to achieve benefit
Treatment: Percutaneous therapy
Target area remote: Yes, radiating pain
Operant and dosage used: Ozone total of 30ml ozone at [30µg/ml] per treatment
Number of treatments: 3
Number of needles: 6
Other medications: Digesic and Voltaren
Clinical overview: There is increased flow of blood to the left lower limb which is particularly vascular in the dorsal subtalar compartment and has mild enthesitis at the TP and TA enthesis was well as anterior capsular enthesitis at the talo-navicular (TN) articular insertion. There is lesser but similar enthesitis and inflammatory arthropathy in the dorsal meta-tarso-phalageal (MTP) articulation. The planar aspect of this joint is relatively unaffected as are the sesamoid bone.

Clinical outcome: The patient recorded a 10 on the pain scale prior to treatment and recorded a 3 on the pain scale at die conclusion of treatment. The patient reported a reduction in the need for digesic for pain management. A complete clearance of infection was achieved commensurate with the cessation of antibiotics. The patient health was adequate such that they could return to work.
Example 7

Patient presented with chronic groin pain. No history of sinister or malignant disease.
Diagnostic imaging by co-registered computer tomography validated molecular imaging (CCTV-MI) was performed and assessment of the obtained images showed synovitis of the right hip joint, lumbosacral and sacroiliac accumulation which is high in activity and mild L5 nerve root neuritis bilaterally as highlighted in figures 7.1, 7.4, 7.5 and 7.6. Figures 7.2 and 7.3 show that all itemised levels would appear as normal on CT images. By way of visualizing, the target area for the delivery of the operant was identified at the right hip and low lumbar spine (L5 perineural bilaterally) and right hip joint were treated.

Age: 71 years old
Gender: Male

Type and dosage of radiopharmaceutical administered during imaging: 700 MBq of (99mTc)-HDP
Anatomical location: T1, T2, T4, T5, T7, T9. Chronic groin pain syndrome and lower back pain, seeing a sports medicine physician for "groin strain". The patient presented with chronic groin pain syndrome and lower back pain.

Sites of delivery of operant: L5 perineural bilaterally, right hip joint and sacroiliac joint

Diagnosis: Synovitis right hip joint, lumbosacral and sacroiliac accumulation which is high in activity and mild L5 nerve root neuritis bilaterally

1. Non-invasive sacroilitis "amas"
2. Right hip synovitis "araas"

Treatment: Percutaneous therapy of left lower hip and low lumbar spine
Target area remote: Yes, radiating lower back pain, extending down legs
Operant and dosage used: 60ml ozone at [25µg/ml]

Number of treatments: 3
Number of needles: 6
Other medications: Steroid injection to groin region with no positive benefit

Clinical overview: Moderate synovitis of right hip joint. There is a concomitant accumulation at the low lumbar spine and sacroiliac joints. Occult or cryogenic pain syndrome was treated and a positive result was achieved.

Clinical outcome: The patient recorded a 10 on the pain scale prior to the commencement of treatment and recorded a 2 on the pain scale at the conclusion of treatment. The patient was no longer in severe pain and enjoyed an improved quality of life.
Example 8

Patient presented with diffuse abdominal pain. No history of sinister or malignant disease.
Non-specific amas identified at large and small gut. Colonoscopy found no abnormality in bowel or terminal ileum.

Diagnostic imaging by X-ray computed tomography (X-ray CT) was performed and assessment of the obtained images showed right sided, contiguous small and large bowel inflammation as highlighted in figures 8.2, 8.3, 8.4 and 8.8. Figures 8.1, 8.5 to 8.7, 8.9 and 8.10 show an amas in the large bowel, identified by a loss of clarity, thickening of the bowel wall with stranding of the myofascial planes.

Age: 62 years old
Gender: Female
Type and dosage of radiopharmaceutical administered during imaging: 600 MBq of \(^{99m}\text{Tc}\)HDP
Anatomical location: Abdomen/pelvis, bowel - large and small
Sites of delivery of operant: The terminal ileum and caecum were sites of delivery
Diagnosis: Inflammatory bowel, amas "congestion" colon and small gut
Treatment: Percutaneous therapy
Target area remote: Yes, general abdominal pain. Cryptogenic diffuse abdominal pain, right flanks, periumbilical and hypergastric pain
Operant and dosage used: 30ml ozone at [30 g/ml] and 30 ml H_2O_2 at [0.5%]
Number of treatments: 3 (after three treatments the pain was completely remediated)
Number of needles: 12
Other medications: Aspirin and codeine

Clinical overview: Small and large bowel inflammation. No regional lymphadenopathy nor mass lesion though multiple tiny nodes as seen in the mesocolon.

Clinical outcome: The patient recorded a 10 on the pain scale prior to the commencement of treatment and recorded a 2 at the conclusion of treatment. Completely off pain medication and the inflammatory bowel was significantly improved and the patient was able to eat a normal diet.

Example 9

Patient presented with general abdominal pain. No history of sinister or malignant disease.
Diagnostic imaging by X-ray and X-ray - CT of the abdomen was performed and assessment of the obtained images showed inflammatory bowel disease as highlighted in figures 9.1 and 9.2.
The features of the amas have been visualised prospectively on non co-registered CT images and appear as subtle smudges and losses of clarity of the myofascial fat planes.

Age: 74 years old
Gender: Female
Anatomical location: Colon
Sites of delivery of operant: The hepatic flexure was injected
Diagnosis: inflammatory bowel disease - amas of the large bowel
Treatment: Percutaneous therapy ozone into the amas and into the peritoneum.

Target area remote: Yes, general abdominal pain. The pain was midline and the lesion "amas" was located on the left side
Operant and dosage used: 30ml ozone at [35ug/ml]
Number of treatments: 3
Number of needles: 16
Other medications: Codeine and morphine patches

Clinical overview: Inflammatory bowel disease or ischemia is the likely cause of the left sided cobblestoning and thickening of the bowel wall. Crohn's disease appears to be associated with amas formation. The patient was looking at surgical re-section but achieved "clinical remission" with treatment trial using ozone.

Clinical outcome: The patient recorded a 9 on the pain scale prior to the commencement of treatment and recorded a 4 on the pain scale post-treatment. The patient is completely off morphine patches and dietary normalisation has been achieved.

Example
Patient presented with general pelvic pain for investigation. No history of sinister or malignant disease.

Diagnostic imaging by X-ray and X-ray - CT was performed and assessment of the obtained images showed an amas of the uterine body and fundus indicative of pelvic inflammatory disease as highlighted in figures 10.1 and 10.2 (Figure 10.2 is an inversion of Figure 10.1 further illustrating the amas identified in Figure 10.1). The features of the amas have been visualised prospectively on non co-registered CT images and appear as subtle smudges and losses of clarity of the myofascial fat planes.

Age: 34 years old
Gender: Female
Anatomical location: Uterus

Sites of delivery of operant: The endometrium was injected

Diagnosis: Pelvic inflammatory disease, endometriosis (amas)

Treatment: Percutaneous therapy

Target area remote: Yes, general pelvic pain

Operant and dosage used: 30ml ozone at [75μg/ml] resulted in cure within 48 hrs

Number of treatments: 3

Number of needles: 3

Other medications:
1. Fadigyn had been used prior and were continued
2. Amoxyl had been used prior and were continued

Clinical overview: The patient had previously used antibiotics without effect. Radiating pain. Uterine infection following delivery of baby.

Clinical outcome: The patient was febrile and toxic prior to treatment with a rapid return to wellbeing and good health. Cessation of antibiotics and an excellent outcome was achieved.

Example 1

Patient presented with abdominal pain and bloating.

Diagnostic imaging by X-ray and X-ray - CT was performed and assessment of the obtained images showed adhesions in the right iliac fossa but no evidence of gut obstruction. The features of the amas have been visualised prospectively on non co-registered CT images and appear as subtle smudges and losses of clarity of the myofascial fat planes. Rapid improvement in symptoms over 3 weeks was achieved. See Figures 11.1 and 11.2 (Figure 11.2 is an inversion of Figure 11.1, further illustrating the amas identified in Figure 11.1).

Age: 48 years old

Gender: Female

Anatomical location: Small bowel

Sites of delivery of operant: The terminal ileum was injected

Diagnosis: Amas identified in the terminal ileum

Treatment: Percutaneous therapy

Target area remote: Yes, radiating abdominal pain

Operant and dosage used: 30ml ozone at [25μg/ml] and 30ml H₂O₂ at [0.5%]

Number of treatments: 3
Number of needles: 6
Other medications: Narcotics and antispasmodics for pain management

Clinical Overview: Subjective adhesions in the right iliac fossa but no evidence of gut obstruction. Incidental fatty infiltration of the liver but otherwise normal, in particular, hernia orifices clear. Although there is diffuse fatty infiltration of the liver, there is minimal evidence of hepatic enlargement and no splenomegally, irregularity nor ascites. Crohn's disease of the terminal ileum.

Clinical outcome: The patient ceased antispasmodics immediately post-treatment and diet renormalisation was achieved over the 3 week period of treatment. The patient recorded a 10 on the pain scale prior to treatment and recorded a 0 on the pain scale post-treatment.

Example 12
Patient presented with radiating abdominal pain for investigation.

Diagnostic imaging by co-registered computer tomography validated molecular imaging (CCTV-MI) was performed and assessment of the obtained images showed metastatic bowel cancer. No metastatic disease within bone. Pathologic uptake within liver metastases is visible and the right renal unit is displaced somewhat downward by the enlarged liver as highlighted in figures 12.1, 12.2, 12.3, 12.4, 12.6, 12.7 and 12.8. Figure 12.5 is an inversion of Figure 12.1 further illustrating the liver metastases highlighted in Figure 12.1.

Age: 62 years old
Gender: Female
Type and dosage of radiopharmaceutical administered during imaging: 700 MBq of \( ^{99m} \text{Tc} \)-HDP

Anatomical location: Ascending colon
Sites of delivery of operant: The parts of the colon and/or the tumour that were injected were the hepatic flexure of the colon and the liver
Diagnosis: Tumour of the ascending colon
Treatment: Percutaneous therapy

Target area remote: Yes, radiating abdominal pain
Operant and dosage used: ozone 60ml ozone at [80ug/ml] per needle
Number of treatments: 5
Number of needles: 12
Other medications: unknown
Clinical overview: Back pain for investigation with the discovery of metastatic liver disease from primary carcinoma of the hepatic flexure of the colon.

Clinical outcome: The patient experienced a relative reduction in pain from 10 at the commencement of treatment to 7 at the conclusion. The patient was able to be managed off narcotics.

Example 13.
Patient presented with Methicillin-resistant Staphylococcus aureus (MRSA) infection in both thighs.

Diagnostic imaging by co-registered computer tomography validated molecular imaging (CCTV-MI; "gallium scan") was performed and assessment of the obtained images showed clinical evidence of quadrieps myositis. The 2 foci noted were promptly treated with antimicrobial therapy as highlighted in Figures 13.1 and 13.4. Figures 13.2, 13.3 and 13.5 to 13.7 further illustrate the extent of the amas identified in Figures 13.1 and 13.4.

Age: 61 years old
Gender: Female
Type and dosage of radiopharmaceutical administered during imaging: 500 MBq of $^{99mTc}$-HDP and 200 MBq of $^{68}$Ga

Anatomical location: Bilateral thighs and pelvic infection/abscesses due to MRSA infection
Sites of delivery of operant: Both thighs and prosthetic joint were injected on separate occasions. The operants were delivered to the thighs antero-laterally and to the hip prosthesis via the buttocks.
Diagnosis: MRSA in both thighs. The patient had been treated with antibiotics for over a year without resolution.

Treatment: Percutaneous therapy
Target area remote from site of pain: Yes, cervical spine pain
Operant and dosage used: 30 ml ozone at [80ug/ml] and 50 ml $\text{H}_2\text{CO}_3$ at [0.5%]
Number of treatments: 12
Number of needles: 36
Other medications: Narcotics for pain management. Rifamycin, Tetracycline. (Chloramphenicol previously and vancomycin recently)

Clinical overview: Extensive MRSA in both thighs, treated with a combination of operants.

Clinical outcome: In this case a MRSA species in a prosthetic joint was treated. The infection continued to debilitate and almost had fatal consequences for the patient as the infected joint could not be surgically
removed. Previous treatment of the infection with antibiotics over the period of several years was unsuccessful in overcoming the infection. After treatment of the target areas identified in the accompanying drawings with ozone, the patient was able to undergo surgical replacement of the infected joint without great concerns of reigniting the infection. The patient does not require any further antibiotics and looks well for the first time in years.

Example 14
9 cancer patients having a variety of solid tumours were treated by direct injection of ozone into the tumour (i.e. a target area identified according to a preferred embodiment of the invention) and the reduction in tumour size in response to the treatment was recorded over varying time intervals. As can be seen from the graphical representation of the data (Figure 14.1) and as summarised below in Table 1, all but one tumour reduced in size over the course of treatment.

<table>
<thead>
<tr>
<th>Initial tumour size (mm) at start of treatment</th>
<th>Dosage of ozone administered</th>
<th>Number of treatments / time period</th>
<th>Follow up tumour size (mm) after treatment</th>
<th>Age of patient (years)</th>
<th>Follow up after</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>60ml of ozone at [80 µg/ml]</td>
<td>9 / 6 months</td>
<td>28</td>
<td>89</td>
<td>12 months</td>
</tr>
<tr>
<td>15</td>
<td>60ml of ozone at [80 µg/ml]</td>
<td>6 / 3 months</td>
<td>3</td>
<td>77</td>
<td>4 months</td>
</tr>
<tr>
<td>18</td>
<td>60ml of ozone at [90 µg/ml]</td>
<td>3 / 3 months</td>
<td>15</td>
<td>79</td>
<td>3 months</td>
</tr>
<tr>
<td>32</td>
<td>60ml of ozone at [80 µg/ml]</td>
<td>8 / 6 months</td>
<td>14</td>
<td>89</td>
<td>7 months</td>
</tr>
<tr>
<td>11</td>
<td>60ml of ozone at [80 µg/ml]</td>
<td>6 / 3 months</td>
<td>3</td>
<td>83</td>
<td>5 months</td>
</tr>
<tr>
<td>12</td>
<td>60ml of ozone at [70 µg/ml]</td>
<td>4 / 1 month</td>
<td>11</td>
<td>72</td>
<td>2 months</td>
</tr>
<tr>
<td>10</td>
<td>60ml of ozone at [80 µg/ml]</td>
<td>7 / 4 months</td>
<td>4</td>
<td>77</td>
<td>6 months</td>
</tr>
<tr>
<td>15</td>
<td>60ml of ozone at [80 µg/ml]</td>
<td>4 / 4 months</td>
<td>6</td>
<td>80</td>
<td>6 months</td>
</tr>
<tr>
<td>21</td>
<td>60ml of ozone at [80 µg/ml]</td>
<td>4 / 6 months</td>
<td>15</td>
<td>81</td>
<td>12 months</td>
</tr>
</tbody>
</table>
It will be appreciated that the illustrated methods of prophylaxis or treatment of disease or treatment of trauma may in certain embodiments provide more effective identification, treatment and palliation of the underlying causes of the syndromes thereby avoiding inefficient, high-cost, extended treatment regimes with expensive and often dependence-inducing drugs.

It will further be appreciated that the illustrated methods of treating a tumour may in certain embodiments provide for direct injection of a therapeutic operant into a cancerous tumour, thereby avoiding detrimental effects of the operant on non-cancerous cells leading to severe physiological and psychological suffering of the subject being treated.

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 method of identifying a target area for the delivery of a prophylactic or therapeutic operant, wherein said target area is in tissue which is substantially not bone tissue, said method including the steps of:
   (a) Scanning a subject, or one or more portions of said subject, using anatomical imaging selected from X-ray computed tomography (CT), sectional imaging ultrasound and Magnetic Resonance Imaging (MRI) in combination with a signal from a molecular bone scan to obtain a co-registered image of said subject or said one or more portions of said subject; and
   (b) Truncating the signal of said molecular bone scan in said co-registered image such that visibility of said signal in said image is enhanced in the target area.

2. A method of identifying a target area for the delivery of a prophylactic or therapeutic operant in an image of a subject, or of one or more portions of said subject, wherein said image is obtained by scanning said subject, or one or more portions of said subject, using anatomical imaging selected from X-ray, X-ray computed tomography (CT), sectional imaging ultrasound and Magnetic Resonance Imaging (MRI), and wherein said target area is determined by a loss of clarity/contrast of a soft-tissue plane.

3. The method according to claim 1 wherein said anatomical imaging is X-ray CT and wherein said molecular bone scan is a Single Photon Emission Computed Tomography (SPECT) scan detecting radiation emitted from a radiopharmaceutical.

4. The method according to claim 3 wherein said SPECT scan detects gamma radiation emitted from a radiopharmaceutical comprising technetium-99m (\(^{99m}\text{Tc}\))-phosphonate/phosphate.

5. The method according to claim 4 wherein said \(^{99m}\text{Tc}\)-phosphonate/phosphate is selected from hydroxymethane diphosphonate (HDP) and methylene hydroxyl diphosphonate (MDP).
6. The method according to claim 4 or 5 wherein said radiopharmaceutical is administered to said subject prior to said scanning at a dosage ranging from about 50 MBq to about 1200 MBq.

7. The method according to claim 6 wherein said dosage ranges from about 50 MBq to about 500 MBq.

8. The method according to any one of the preceding claims wherein said target area is in tissue which is substantially soft tissue.

9. The method according to claim 8 wherein said target area in said soft tissue is substantially at the soft tissue-bone tissue boundary.

10. A method for identifying a target area, substantially as herein described with reference to the examples but excluding comparative examples.

11. A method of prophylaxis or treatment of pain or a disease or a method of treatment of trauma, said method including the steps of identifying a target area according to the method defined in any one of claims 1 to 10 and delivering a therapeutically effective amount of an operant to said target area.

12. The method according to claim 11 wherein said target area is substantially remote from a site of pain, disease or trauma.

13. The method according to claim 11 or claim 12 wherein said pain is caused by a pain syndrome.

14. The method according to claim 13 wherein said pain syndrome is selected from the group consisting of complex pain syndrome; chronic pain syndrome; regional pain syndrome; relapsing pain syndrome; loco-regional pain syndrome; acute or chronic pain syndrome; amorphous pain syndrome; deep pain syndrome; recurrent pain syndrome; remitting pain syndrome; resistant pain syndrome; shooting pain syndrome; sharp pain syndrome; electric pain syndrome; evanescent pain syndrome; benign pain syndrome; malignant pain syndrome; parenchymal pain syndrome; integumentary pain syndrome;
occult or otherwise hidden or obtuse pain syndrome; forensic pain syndrome; complex regional pain syndrome; compensational pain syndrome; prosthetic pain syndrome; peri-prosthetic; pain syndrome referred pain syndrome; atypical pain syndrome; post-surgical pain and phantom pain syndrome.

15. The method according to claim 13 or claim 14 wherein said pain syndrome is caused by nerve root compression, disk herniation and/or sciatica.

16. The method according to claim 11 wherein said disease causes inflammation.

17. The method according to claim 16 wherein said inflammation is periarthritis, tendonopathy, peritenonitis, neuritis, enthesitis, symphysitis, myositis, myotendonitis, pericarditis, mesothelial inflammation, serositis, adventitial inflammation, periarteritis, or arteritis.

18. The method according to claim 11 wherein said disease is caused by an orthodox treatment-resistant infection.

19. The method according to claim 18 wherein said orthodox treatment resistant infection is a Methicillin-resistant Staphylococcus aureus (MRSA) infection.

20. The method according to claim 18 or claim 19 wherein said therapeutically effective amount of said operant is delivered to said target area by direct injection of said operant into said target area.

21. The method according to any one of the preceding claims wherein said operant is ozone.

22. The method according to any one of claims 11 to 20 wherein said operant is ozone and said therapeutically effective amount of said ozone ranges from about 10 ml to about 40 ml of ozone at a concentration ranging from about 0.01 ug/ml to about 1000 ug/ml.

23. The method according to claim 22 wherein said therapeutically effective amount of said ozone ranges from about 10 ml to about 100 ml of ozone at a concentration ranging from: about 1 ug/ml to about 40 ug/ml, preferably 25 ug/ml, for the treatment of pain;
about 1 ug/ml to about 60 \( \mu g/ml \), preferably 30 \( \mu g/ml \), for the treatment of inflammation; about 20 ug/ml to about 120 ug/ml, preferably 90 \( \mu g/ml \), for the treatment of tumours; about 1 ug/ml to about 25 ug/ml, preferably 15 \( \mu g/ml \), for the treatment of ischemia; about 1 \( \mu g/ml \) to about 25 \( \mu g/ml \), preferably from about 5 \( \mu g/ml \) to 15 \( \mu g/ml \), to effect beneficial immune-modulation and/or immune adaptation; or about 1 \( \mu g/ml \) to about 25 \( \mu g/ml \), preferably 5ug/ral, to effect enhanced graft take.

24. The method according to claim 11 wherein said step of delivering a therapeutically effective amount of said operant to said target area includes inhaled delivery, ingested delivery, percutaneous delivery, per rectal delivery, per mucosal delivery, per nasal delivery, per optic delivery, trans-cutaneous delivery, trans-visceral delivery, trans-mucosal delivery, insufflation delivery, pleotherapy delivery, hyperbaric delivery, isobaric delivery or hypobaric delivery.

25. The method according to claim 24 wherein said step of delivering a therapeutically effective amount of said operant includes injection of said operant.

26. A method of prophylaxis or treatment of pain or a disease or a method of treatment of trauma, substantially as described herein with reference to the examples but excluding comparative examples.

27. A method of identifying a direct injection target area for direct injection of a therapeutic operant in an image of a subject or of one or more portions of said subject, wherein said image is obtained by scanning said subject, or one or more portions of said subject, using anatomical imaging selected from X-ray computed tomography (CT), sectional imaging ultrasound and Magnetic Resonance Imaging (MRI), and wherein said target area is determined by a loss of clarity/contrast of a soft-tissue plane.

28. The method according to claim 27 wherein said direct injection target area is in tissue which is substantially not bone tissue, and wherein said image is a co-registered image of said subject or said one or more portions of said subject obtained by scanning said subject, or said one or more portions of said subject, using anatomical imaging selected from X-ray computed tomography (CT), sectional imaging ultrasound and Magnetic Resonance Imaging (MRI) in combination with a signal from a Positron Emission
Tomography (PET) scan, and wherein said target area is further determined by truncating the signal of said PET scan in said co-registered image such that visibility of said signal in said image is enhanced in the target area.

29. The method according to claim 28 wherein said anatomical imaging is X-ray CT and wherein said PET scan detects radiation emitted from a radiopharmaceutical.

30. The method according to claim 29 wherein said PET scan detects positrons emitted from a radiopharmaceutical comprising fluorine-18 (¹⁸F-PET) fluorodeoxyglucose (FDG-PET).

31. A method for identifying a direct injection target area, substantially as herein described with reference to the examples but excluding comparative examples.

32. A method of treating a tumour comprising administration of a therapeutic operant to a direct injection target area identified according to one of the methods of claims 27 to 31.

33. The method according to claim 32 wherein said tumour is a cancerous tumour.

34. The method according to claim 32 or 33 wherein said administration is direct injection into said target area.

35. The method according to any one of claims 32 to 34 wherein said therapeutic operant is ozone.

36. The method according to claim 32 wherein said therapeutically effective amount of said ozone ranges from about 10 ml to about 40 ml of ozone at a concentration ranging from about 0.01 μg/ml to about 1000 ug/ml.

37. The method according to claim 36 wherein said therapeutically effective amount of said ozone ranges from about 20 μg/ml to about 120 ug/ml, preferably 90 ug/ml.
38. A method of treating a tumour substantially as herein described with reference to the examples but excluding comparative examples.

39. A method of treating a dysadaptive or dysfunctional illness comprising administration of a therapeutic operant to a direct injection target area identified according to any one of the methods of claims 27 to 31.

40. The method according to claim 39 wherein said dysadaptive or dysfunctional illness is caused by toxicity, metabolic imbalance, trauma such as a burn, ischemia, hyperimmunity, autoimmunity, innate immunity, transplant rejection, adaptive immunity, infection, inflammation, degeneration, incomplete regeneration, incomplete hybrid vigour or incomplete wellness.

41. A method of treating a dysadaptive or dysfunctional illness substantially as herein described with reference to the examples but excluding comparative examples.
Figure 6.3

[Diagram of foot with labels and annotations]
Figure 7.5
Figure 8.4
Figure 14.1

Reduction of tumour size in response to direct ozone injection

- 9 treatments of 60ml ozone at [90 μg/ml]
- 6 treatments of 60ml ozone at [80 μg/ml]
- 3 treatments of 60ml ozone at [90 μg/ml]
- 8 treatments of 60ml ozone at [90 μg/ml]
- 6 treatments of 60ml ozone at [90 μg/ml]
- 4 treatments of 60ml ozone at [70 μg/ml]
- 7 treatments of 60ml ozone at [80 μg/ml]
- 4 treatments of 60ml ozone at [80 μg/ml]
- 4 treatments of 60ml ozone at [80 μg/ml]
INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU20 11/000 109

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.
A61N 5/00 (2006.0 1) .46/5 6/00 (2006.0 1)
A61B 5/00 (2006.0 1) A61B 5/00 (2006.0 1)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of database and, where practicable, search terms used)

EPDOCA, W/PI: IPC & ECLA A 6 1N5, A 6 1N7, A 6 1B5, A 6 1B6, A 6 1B8 & Keywords (CT, MRJ, ultrasound, SPECT, co_regis+ , image, truncate+) and like terms

Google, Google Scholar and Google Patent & Keywords (CT, MRJ, ultrasound, SPECT, ozone) and like terms

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C

Date of actual completion of the international search 23 March 2011
Date of mailing of the international search report 25 MAR 2011

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Form PCT/ISA/2 10 (second sheet) (July 2009)
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**INTERNATIONAL SEARCH REPORT**

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

2. **Claims Nos.: 10 and 26**
   - because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
     - Claims 10 and 26 do not comply with Rule 6.2 (a) because they rely on references to the examples.

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

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

See Supplemental Box 1

1. **As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.**
2. **As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.**
3. **As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:**

4. **No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1 and 3-26**

**Remark on Protest**

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.
Supplemental Box 1
(To be used when the space in any of Boxes I to IV is not sufficient)

Continuation of Box No: III

This International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

In assessing whether there is more than one invention claimed, I have given consideration to those features which can be considered to potentially distinguish the claimed combination of features from the prior art.

This International Searching Authority has found that there are different inventions as follows:

- Claims 1 and 3-26 relate to a method of identifying a target area for the delivery of a prophylactic or therapeutic operand, wherein the target area is tissue which is substantially not bone tissue, said method includes (a) scanning a subject using anatomical imaging selected from X-ray computed tomography (CT), sectional imaging ultra sound, and Magnetic Resonance Imaging (MRI) in combination with a molecular bone scan to obtain a co-registered image of the subject or one or more portions of the subject and (b) truncating the signal of molecular bone scan in co-registered image such that signal of molecular bone scan remains visible in image in the target area.

  It is considered that combining a molecular bone scan to obtain a co-registered image of the subject or one or more portions of the subject and (b) truncating the signal of molecular bone scan in coregistered image such that signal of molecular bone scan remains visible in image in the target area define a first invention.

- Claims 2 and 27-41 relate to a method of identifying a target area for the delivery of a prophylactic or therapeutic operand wherein the image is obtained by scanning a subject, or one or more portions of the subject using anatomical imaging selected from X-ray, X-ray computed tomography (CT), sectional imaging ultra sound and Magnetic Resonance Imaging (MRI), and wherein target area is determined by a loss of clarity/contrast.

  It is considered that the target area being determined by a loss of clarity/contrast of a soft-tissue plane define a second invention.

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art.

None of the abovementioned groups of claims share any special technical feature. Because there is no common special technical feature it follows that there is no technical relationship between the identified inventions. Therefore the claims do not satisfy the requirement of unity of invention apriori.

I have limited the search and report to the invention defined by 1 and 3-26 because of lack of unity apriori.

NOTE: Claims 10 and 26 are not searched as they do not comply with Rule 6.2 (a). See Box II
This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX