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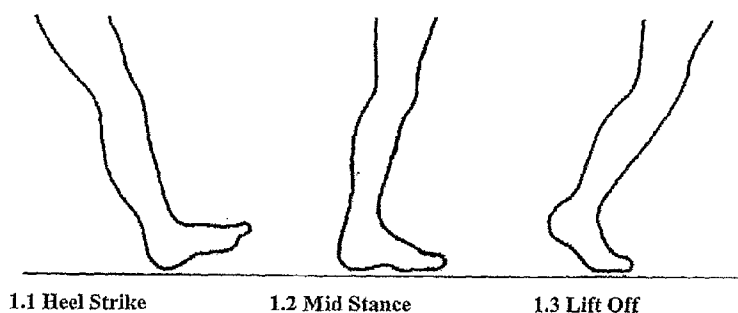
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(54) Title: IN VIVO STIMULATION OF CELLULAR MATERIAL



1.4



(57) Abstract: The present invention relates to the in vivo stimulation of cellular material. In particular, the present invention relates to a method for stimulating cells and tissue in vivo comprising the step of applying to said cells and tissue an electrobiomimetic stimulus, wherein the growth characteristics of said cells and tissue are enhanced as compared to cells and tissue not receiving said stimulus.

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In vivo Stimulation of Cellular Material

Field of the Invention

5 The present invention relates to the *in vivo* stimulation of cellular material. In particular, the present invention relates to a method for stimulating cells and tissue *in vivo* comprising the step of applying to said cells or tissue a stimulus which promotes cellular activity.

10

Background of the Invention

Use of electromagnetic field pulses (EMFP) for the treatment of chronic disorders like arthritis, tendonitis
15 and inflammation are well known. See, for example, US. Pat. Nos 5,376,065, 4,266,532, 4,461,663, 4,535,775, 3,890,953, 3,893,462, 3,952,751 and 4,667,809. In some of these previously described methods, a section of the body to be treated, such as a limb, is placed inside an annular
20 coil. EMFP are then applied within clinically usable frequencies in order to produce endogenous regeneration by stimulating cartilage and/or connective tissue. See, for example, US Pat. Nos. 3,270,746, 3,329,149 and 3,952,751. It is to be understood that the above described methods
25 are reflective of the efforts in the prior art to employ bursts of EMFP in the megahertz range, as opposed to other efforts in the prior art, which employ bursts of pulses of electromagnetic waves which are in the kilohertz range or lower.

30

In the past ten years, relatively high frequency EMFP has been used in the treatment of various disorders (see, for example, US Pat. Nos. 4,454,882, 4,674,482, 4,998,532 and 5,014,699). Also in recent years the clinical use of EMFP
35 at radio frequencies has been used. In these areas pulse bursts having sinusoidal or other form have been used. The frequency used is often around 27 MHz with each pulse

burst typically exhibiting a width of sixty-five microseconds and containing a range of 1,100 to 10,000 pulses per burst, and with a pulse burst repetition rate in the range of 0.01 to 1,000 Hertz.

5

However, while there has been a large amount of research in the use of EMFP for the treatment of a number of disorders, there still remains a high degree of uncertainty regarding the most effective parameters that can be used for treatment. This is illustrated by the numerous patents reflect the plethora of possible parameters that have been trialled (see, US. Pat. No. 4,467,808 which utilizes a 20-100 KHz signal generated by an alternating current power supply for the treatment of osteoporosis in bone; US. Pat. Nos. 4,266,532 and 4,461,663 which describe the use of unidirectional low voltage pulses; and US. Pat. No. 4,535,775, which describes a non-invasive capacitor-coupled signal.

Consequently, it can be seen that there remains a continuing need for a therapeutic regime for the use of EMFP *in vivo* that correctly identifies clinically useful parameters.

25 Summary of the Invention

The inventors have shown that by the application of exogenous EMFP, which mimics the effects of real physical exercise, it is possible to treat cells, tissue and organs *in situ*. In particular, the inventors have determined specific electrobiomimetic stimuli that equate to real physiological conditions associated with exercise.

Accordingly, in a first aspect the present invention provides a method for stimulating cells and tissue *in vivo* comprising the step of applying to said cells and tissue an electrobiomimetic stimulus, wherein the growth

characteristics of said cells and tissue are enhanced as compared to cells and tissue not receiving said stimulus.

5 The electrobiomimetic stimulus comprises a pattern of specifically configured time varying EMFP responsible for the enhanced growth characteristics.

10 In a second aspect, the present invention provides a method for stimulating cells and tissue *in vivo* comprising the step of applying to said cells and tissue an electrobiomimetic stimulus comprising a plurality of time periods, wherein each time period comprises a plurality of electromagnetic field pulse blocks separated by intervals of no electromagnetic field pulses, each electromagnetic
15 field pulse block comprises a plurality of electromagnetic field pulses of defined duration, wherein each electromagnetic field pulse of the plurality of electromagnetic field pulses is separated by a time variable pulse space and wherein said intervals vary in
20 length of time between each period and wherein the duration of the electromagnetic pulses are uniform.

Preferably, the electrobiomimetic stimulus comprises between 2 and 4 time periods, more preferably between 2 and 3 time
25 periods and most preferably three time periods, wherein each time period comprises blocks of electromagnetic field pulse, which are distinct from each other. It will be appreciated by those skilled in the art that the periods are designed to mimic the typical exercise pattern of "warm up", "maximal
30 exercise" and "cool down". In some embodiments, the time periods simulating a gentle walk (period 1), explosive exercise (period 2) and then light jog (period 3), wherein the rate or frequency of delivery of the blocks of electromagnetic field pulse plays an important role.
35 Accordingly, the duration of each time period will be tailored to the desired result and to mimic the exercise pattern outlined above. In some embodiments, the

electrobiomimetic stimulus comprises three time periods, wherein time period 1 has duration of between 2 minutes and 9 minutes, time period 2 has duration between 10 minutes and 18 minutes and time period 3 has duration between 6 minutes and 12 minutes.

It will be appreciated that as the duration of each time period varies the number of electromagnetic field pulse blocks or "patterns" within each time period will also vary.

10 The electromagnetic field pulse blocks are designed to replicate the piezo-electric response observed in fully hydrated connective tissues, when subjected to normal physiological stress levels. Each electromagnetic field pulse block is separated by an interval of no

15 electromagnetic field pulse. The interval separating the electromagnetic field pulse blocks will be of variable time lengths depending upon the treatment requirements. In some embodiments, the interval between each electromagnetic field pulse block in period 1 will be between 14ms and 200ms,

20 while the interval in period 2 will be between 5ms and 80ms and the interval in period 3 between 20ms and 100ms.

It will be appreciated by those skilled in the art that within each electromagnetic field pulse block, there will

25 be a plurality of individual electromagnetic field pulses. Each electromagnetic field pulse provides growth altering characteristics to cells and tissue *in vivo*. As such, any magnetic field intensity may be used as long as it provides growth altering characteristics to cells and

30 tissue. In some embodiments, the magnetic field intensity used is between 1 Gauss to 100 Gauss i.e. between 0.0001T to 0.01T. Preferably, the magnetic field intensity is between about 1 Gauss to 100 Gauss, more preferably 3 Gauss. It will be appreciated that this may also be

35 expressed in the terms of mV per cm. In this instance, the preferred intensity is 1.3mV per cm.

As discussed above, the electromagnetic pulse blocks replicate the piezo-electric response to fully hydrated connective tissues. As such, the duration of each electromagnetic field pulse can vary. Preferably, the pulse
5 duration is between 200µs and 380µs.

Within each electromagnetic pulse block there is a plurality of electromagnetic field pulses. Preferably, the number of electromagnetic field pulses in each block is
10 between 1 and 50, preferably, between 10 and 30, most preferably about 20. In some embodiments, the number of electromagnetic field pulses within each block is 20 and the pulse duration for each pulse is about 100µs.

15 Each electromagnetic field pulse within each block can be spaced by varying time spaces. Typically, the time space between each electromagnetic field pulse is between 0 and 300000µs. In some preferred embodiments, the 20 electromagnetic field pulses have spacings of P1 - 1 to 25500µs; P2 - 0 to 24000µs; P3 - 0 to 22000µs; P4 - 0 to 20000µs; P5 - 0 to 20000µs; P6 - 0 to 20000µs; P7 - 0 to 20000µs; P8 - 0 to 20000µs; P9 - 0 to 22000µs; P10 - 0 to 24000µs; P11 - 0 to 25500µs; P12 - 0 to 24000µs; P13 - 0 to 22000µs; P14 - 0 to 22000µs; P15 - 0 to 24000µs; P16 - 0 to
25 12000µs; P17 - 0 to 15000µs; P18 - 0 to 20000µs; P19 - 0 to 21000µs and P20 - 0 to 22000µs.

In a third aspect the present invention provides a method for treating tissue *in situ* comprising: collecting a
30 selected portion of tissue, and securing said portion of tissue adjacent to an energy transmitting element; transmitting an electrobiomimetic stimulus from said energy transmitting element; and transmitting said electrobiomimetic stimulus to target cells within said
35 portion of tissue until growth characteristics of said cells and tissue are altered as compared to cells and tissue not receiving said stimulus.

In a fourth aspect, the present invention provides a system to treat tissue *in vivo*, the system comprising: an energy source; an energy transmitting element for
5 providing an electrobiomimetic stimulus; and a holding mechanism adapted to hold tissue, such that electrobiomimetic stimulus emitted by said energy transmitting element treats said tissue.

10 In a fifth aspect, the present invention provides a method of treating an individual comprising the steps of: providing a device comprising an electromagnetic field pulse generator; positioning the device adjacent to a
15 bodily tissue of an individual; and operating the device for a duration, at a frequency, and at a peak effective to elicit a therapeutic response in the individual, wherein the device is positioned relative to the individual such that the device induces an electrobiomimetic stimulus within the bodily tissue.

20 Preferably, the individual has a bone, joint, soft-tissue, or connective tissue disorder and the therapeutic response comprises a reduction or elimination of inflammation and/or pain in a bone, joint, soft-tissue, or connective
25 tissue of the individual.

Preferably, the individual has a disorder selected from the group consisting of adhesive capsulitis, tennis elbow, osteoarthritis, back pain, multiple sclerosis, tendon
30 inflammation, and carpal tunnel syndrome, and the therapeutic response comprises a reduction or elimination of inflammation and/or pain associated with the disorder.

Brief Description of the Drawings

35 Figure 1 is a graphical representation of the bioelectrical events recorded in dynamically loaded bone during normal

articulation at walking frequencies of less than 1 cycle per second and with an applied load dynamic of less than 1.5 times body weight.

- 5 Figure 2 is a graphical representation of the bioelectrical events that take place in the region of the tibia in a normal adult during the stages of ambulation.

- Figure 3 is a graphical representation of combinatorial
10 stimuli of bioelectrotherapy signals and other physical parameters applied as a biomimicry signal for the purposes of stimulating specific beneficial processes.

- Figure 4 shows a pictorially representation of a treatment
15 regime for the treatment of an ankle injury.

Figure 5 shows a pictorially representation of a treatment regime for the treatment of done disorders.

- 20 Figure 6 shows a pictorially representation of a treatment regime for the treatment of tennis elbow.

- Figure 7 shows a pictorially representation of a treatment
25 regime for the treatment of hip injury.

Figure 8 shows a pictorially representation of a treatment regime for the treatment of knee injury.

- Figure 9 shows a pictorially representation of a treatment
30 regime for the treatment of lower back strain.

Figure 10 shows a pictorially representation of a treatment regime for the treatment of mid back strain.

- 35 Figure 11 shows a pictorially representation of a treatment regime for the treatment of neck strain.

Figure 12 shows a pictorially representation of a treatment regime for the treatment of osteoarthritis.

Figure 13 shows a pictorially representation of a treatment
5 regime for the treatment of a shoulder injury.

Figure 14 shows a pictorially representation of a treatment regime for the treatment of a vascular disorder.

10 Figure 15 shows a pictorially representation of a treatment regime for the treatment of a wrist injury.

Detailed Description of the Preferred Embodiments

15 Before describing the present invention in detail, it is to be understood that this invention is not limited to particularly exemplified cell culture techniques, serum, media or methods and may, of course, vary. It is also to
20 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 which will be limited only by the appended claims.

All publications, patents and patent applications cited
25 herein, whether supra or infra, are hereby incorporated by reference in their entirety. However, publications mentioned herein are cited for the purpose of describing and disclosing the protocols, reagents and vectors which are reported in the publications and which might be used
30 in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

35 It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates

otherwise. Thus, for example, a reference to "a cell" includes a plurality of such cells, and a reference to "an electrobiomimetic pulse" is a reference to one or more pulses, and so forth. Unless defined otherwise, all
5 technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any materials and methods similar or equivalent to those described herein can be used to practice or test the
10 present invention, the preferred materials and methods are now described.

The broadest aspect of the present invention relates to a method for stimulating cells and tissue *in vivo* by
15 applying an electrobiomimetic stimulus.

The term "*in vivo*" as used herein specifically refers to the stimulation of cells and tissue within the body of an individual or animal. The terms "stimulation" and
20 "stimulating" as used herein interchangeably means that the electrobiomimetic stimulus affects the cells or tissue of the animal such that the "growth characteristics" of these cells are enhanced relative to cells or tissue not stimulated by the electrobiomimetic stimulus of the
25 present invention. The enhanced growth of cells and tissue can be readily determined by persons skilled in the art.

The term "electrobiomimetic stimulus" as used herein
30 refers to a time varying stimulus that is produced by an electromagnetic field pulse, which mimics the bioelectrical effects produced by cells and tissue during real physical exercise.

35 It will be appreciated by those skilled in the art that the electrobiomimetic stimulus comprising an electromagnetic field pulse (EMFP) can be of any magnetic

field intensity so long as it provides an alteration in the growth characteristics of *in vitro* cultured cells. In some embodiments, the magnetic field intensity is between about 1 Gauss to about 100 Gauss i.e. between 0.001 μ T to 1 μ T, preferably 3 gauss and of such flux as to induce between 1.0 and 2.0 mv/cm, preferably 1.4 mv/cm of free standing conductor.

In this regard, it should be noted that the International System (SI) unit of field intensity for magnetic fields is Tesla (T). One tesla (1 T) is defined as the field intensity generating one newton of force per ampere of current per meter of conductor:

$$T = \text{Nw} \cdot \text{A}^{-1} \cdot \text{m}^{-1} = \text{kg} \cdot \text{s}^{-2} \cdot \text{A}^{-1}$$

However, certain other non-SI units, like Gauss (G), are interchangeably used herein. Some are important for the interpretation of older scientific texts, but their use is not encouraged. Table 1 shows the conversion factors from one unit to another:

Tesla (T)	Microtesla (μ T)	Gauss (G)	Miligauss (mG)
1	1000000	10000	10000000
0.000001	1	1000	10
0.0001	0.001	1	1000
0.0000001	0.01	0.001	1

The term "time varying" as used herein refers to the phenomena where the patterns of electrobiomimetic stimulus are delivered to the cells, tissue and organs *in situ* for varying lengths of time depending upon the requirements for the treatment.

The present invention functions through the stimulation of

specific and predictable bioresponse in the major joints of an individual's body through the simulation of the bio-electro-phenomena induced in connective tissues by real physical activity.

5

In order to provide the optimum biomimetic stimuli to encourage the resolution of common injury and overuse pathologies in various joints and tissue groups of the body, specifically configured time varying electromagnetic fields
10 pulses have been developed by the present inventors to mimic those produced in those tissue groups by exercise of the maximum benefited nature.

As described *supra* and *infra*, the electrobiomimetic
15 stimulus comprises a number of time periods comprising blocks of electromagnetic field pulse, which are distinct from each other. These time periods are designed to mimic the typical exercise pattern of "warm up", "maximal exercise" and "cool down". In some embodiments, the time
20 periods simulating a gentle walk (period 1), explosive exercise (period 2) and then light jog (period 3), wherein the rate or frequency of delivery of the blocks of electromagnetic field pulse plays an important role.

25 The duration of each time period will be tailored to the desired result. For example, as described in examples 1 to 12 *infra*, different joints, body parts and like will require slightly different time periods. However, generally there are three time periods, where the first
30 time period (period 1) has duration of between 2 minutes and 9 minutes, the second time period (period 2) has a duration of between 10 minutes and 18 minutes and the third time period (period 3) has a duration between 6 minutes and 12 minutes.

35

The electromagnetic field pulse blocks or "patterns" within each time period can also vary. The electromagnetic field

pulse blocks are designed to replicate the piezo-electric response observed in fully hydrated connective tissues, when subjected to normal physiological stress levels. Each electromagnetic field pulse block is separated by an interval of no electromagnetic field pulse. The interval separating the electromagnetic field pulse blocks will be of variable time lengths depending upon the treatment requirements. In some embodiments, the interval between each electromagnetic field pulse block in period 1 will be between 14ms and 200ms, while the interval in period 2 will be between 5ms and 80ms and the interval in period 3 between 20ms and 100ms.

Once a particular treatment regime has been devised an individual is treated using the electrobiomimetic stimuli. The term "individual" as used herein refers to any member of the class mammalia, including, without limitation, humans and other primates, including non-human primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, sheep, pigs, goats and horses; domestic mammals such as dogs and cats; laboratory animals including rodents such as mice, rats and guinea pigs. The terms do not denote a particular age. Thus, both adult and newborn individuals are intended to be covered.

Thus, provided is the treatment of mammals such as humans, as well as those mammals of economical importance and/or social importance to humans, for instance, carnivores other than humans (such as cats and dogs), swine (pigs, hogs, and wild boars), ruminants (such as cattle, oxen, sheep, giraffes, deer, goats, bison, and camels), and horses.

Generally, the terms "treating," "treatment," "healing" and the like are used herein to mean affecting an individual or subject, their tissue or cells to obtain a desired pharmacological and/or physiological effect. The effect

is generally therapeutic in terms of partial or complete cure of a bone, joint, soft-tissue, or connective tissue disorder. "Treating" as used herein covers any treatment of disorder in a mammal, particularly a human, and
5 includes: (a) inhibiting the progression of a bone, joint, soft-tissue, or connective tissue disorder, i.e., arresting its development; or (b) relieving or ameliorating the symptoms of a bone, joint, soft-tissue, or connective tissue disorder, i.e., cause regression of
10 the symptoms of the disorder.

In particular, the therapeutic response will comprise a reduction or elimination of inflammation and/or pain associated with a bone, joint, soft-tissue, or connective
15 tissue of the individual. This will partially be brought about by an enhancement of the growth of cells and tissue.

In some embodiments, the disorder is selected from the group consisting of adhesive capsulitis, tennis elbow, osteoarthritis, back pain, multiple sclerosis, tendon
20 inflammation, and carpal tunnel syndrome, and the therapeutic response comprises a reduction or elimination of inflammation and/or pain associated with the disorder.

25 Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises", is not intended to excluded other additives, components, integers or steps.

30

The invention will now be further described by way of reference only to the following non-limiting figures. It should be understood, however, that the description following is illustrative only, and should not be taken in
35 any way as a restriction on the generality of the invention described above.

Now Referring to Figure 1, there is illustrated, a leg of a normal adult through the stagers of normal ambulation gait in which 1.1 represents the heel strike phase, 1.2 represents the weight transition phase and 1.3 represents the lift-off phase.

1.4 is a graphical representation of the relative changes in frequency of resonance of bioelectrical phenomena observed in the leg during ambulation.

10

The forces of compression applied to the leg vary during the phases of progression within the gait and these forces act to modify the normal frequency of resonance. As physiological processes such as osteogenesis are known to be stimulated by such ambulation the bioresponse observed must dependent on presence of such bioelectrical phenomena and not on a fixed standing stimuli as proposed by McLeod et al in US 5,318,561 and Markoll in US 5,453,073.

20 Additionally, the frequency of resonance of bioelectrical phenomena observed in children are distinctly different from those observed in adults, yet it is well known that physiological processes such as osteogenesis are stimulated by the same real physical exercise. Evidence of such physiological processes being stimulating by such widely varying bioelectrical phenomena indicate that the simple stimuli model of the standing or non varying wave form do not replicate the complex nature of biomimetic phenomena and that only complex stimuli, as disclosed, are capable of mimicking actual bioelectrical phenomena.

Now referring to Figure 2, there is illustrated the bioelectrical phenomena observed in different types of ambulation.

35

2.1 illustrates the typical adult walk of 1 stride or cycle per second during which a load influence of approximately

1.5 times body weight is applied and acts to stimulate physiological processes.

It is generally known that walking, producing the
5 combinatorial patterns of bioelectrical phenomena of
described in 2.1 stimulates a number of beneficial
physiological processes including the dilation of blood
vessels, the masking or modification of the inflammatory
response, the opening of various ATP channels and the
10 release of certain precursor hormones and chemical
messengers.

2.2 illustrates the bioelectrical phenomena observed in
adults in response to a jogging form of ambulation. In the
15 illustrated case, a stride or cycle rate of .8 cycles per
second is used and a compressive force equal to
approximately 2.0 times body weight. Such combinatorial
patterns are known to produce physiological effects
including but not limited to, the eneration of aligning
20 forces that assist in the organization of newly synthesized
biomaterials, the suppression of the immune response and a
relaxation of the metabolic water-binding forces.

2.3 illustrates the bioelectrical phenomena observed in
25 adults in response to a running form of ambulation. In the
illustrated case, a stride or cycle rate of 2.3 cycles per
second is used and a compressive force equal to
approximately 3.0 times body weight. Such complex
combinatorial stimuli patterns are know to stimulate
30 biosynthesis across a range of tissues and at rates
statistically higher than with other complex stimuli
patterns.

Now referring to Figure 3, there is illustrated a form of
35 applied biomimicry in which complex combinatorial forms of
electrotherapy, possibly, but not essentially, of a time
varying electromagnetic type with a combination of

changes in environmental physical parameters such as, but not limited to, temperature, pressure and humidity, are applied to evoke and elicit complex beneficial physiological processes.

5

3.1 illustrates one possible bioelectromimetic type, applied as a biomimicry signal for the purposes of stimulating the dilation of blood vessels, the masking or modification of the inflammatory response, the opening of the various ATP
10 channels and the release of certain precursor hormones and chemical messengers without the cellular trauma and tissue damage associated with real physical exercise.

3.2 illustrates one possible bioelectromimetic form applied
15 as a biomimicry signal for the purposes of stimulating organizational influences for the alignment of newly synthesized biomaterials, the suppression of the immune response and a relaxation of the metabolic water-binding forces without the cellular trauma and tissue damage
20 associated with real physical exercise.

3.3 illustrates one possible bioelectromimetic form applied as a biomimicry signal for the purposes of stimulating biosynthesis without the cellular trauma and tissue damage
25 associated with real physical exercise.

Further details of practicing this inventive subject matter are furnished by way of the following examples which, however, should not be construed so as to impose
30 any kind of limitation to the scope of the invention.

EXAMPLE 1

TREATMENT OF ANKLES

The ankle is subject to specific loads during normal
35 articulation. In order to provide the healthiest physiology to encourage rapid tissue turn-over, electrobiomimetic stimulus was applied as follows:

- 17 -

	Period 1 Duration	8 minutes
	Period 2 Duration	10 minutes
	Period 3 Duration	12 minutes
5	Period 1 Interval	40 ms
	Period 2 Interval	20 ms
	Period 3 Interval	50 ms
	Pulse Duration	300 μ s
	P1 x 100 μ s	200
10	P2 x 100 μ s	100
	P3 x 100 μ s	80
	P4 x 100 μ s	60
	P5 x 100 μ s	40
	P6 x 100 μ s	20
15	P7 x 100 μ s	10
	P8 x 100 μ s	5
	P9 x 100 μ s	5
	P10 x 100 μ s	5
	P11 x 100 μ s	5
20	P12 x 100 μ s	40
	P13 x 100 μ s	60
	P14 x 100 μ s	100
	P15 x 100 μ s	120
	P16 x 100 μ s	120
25	P17 x 100 μ s	140
	P18 x 100 μ s	160
	P19 x 100 μ s	200
	P20 x 100 μ s	200

30 The regime described above is shown pictorially in Figure 1.

EXAMPLE 2

TREATMENT OF BONES

35 Bone is subject to constant and continuous remodelling and osteogenesis is known to be stimulated by exercise. In order to provide the healthiest physiology to encourage rapid bone-growth, electrobiomimetic stimulus was applied as

- 18 -

follows:

	Period 1 Duration	2 minutes
	Period 2 Duration	18 minutes
5	Period 3 Duration	10 minutes
	Period 1 Interval	90 ms
	Period 2 Interval	40 ms
	Period 3 Interval	100 ms
	Pulse Duration	300µs
10	P1 x 100µs	4
	P2 x 100µs	4
	P3 x 100µs	4
	P4 x 100µs	4
	P5 x 100µs	4
15	P6 x 100µs	4
	P7 x 100µs	4
	P8 x 100µs	4
	P9 x 100µs	4
	P10 x 100µs	50
20	P11 x 100µs	50
	P12 x 100µs	50
	P13 x 100µs	50
	P14 x 100µs	50
	P15 x 100µs	50
25	P16 x 100µs	50
	P17 x 100µs	50
	P18 x 100µs	50
	P19 x 100µs	50
	P20 x 100µs	50

30

The regime described above is shown pictorially in Figure 2.

EXAMPLE 3

TREATMENT OF ELBOW

35 The elbow is subject to both overuse and traumatic injuries and combines a range of tissue groups. In order to provide the healthiest physiology to encourage rapid repair and

- 19 -

reductions in inflammation, electrobiomimetic stimulus was applied as follows:

	Period 1 Duration	3 minutes
5	Period 2 Duration	17 minutes
	Period 3 Duration	10 minutes
	Period 1 Interval	100 ms
	Period 2 Interval	14 ms
	Period 3 Interval	75 ms
10	Pulse Duration	300 μ s
	P1 x 100 μ s	255
	P2 x 100 μ s	200
	P3 x 100 μ s	100
	P4 x 100 μ s	90
15	P5 x 100 μ s	80
	P6 x 100 μ s	70
	P7 x 100 μ s	60
	P8 x 100 μ s	50
	P9 x 100 μ s	40
20	P10 x 100 μ s	30
	P11 x 100 μ s	10
	P12 x 100 μ s	11
	P13 x 100 μ s	9
	P14 x 100 μ s	8
25	P15 x 100 μ s	7
	P16 x 100 μ s	6
	P17 x 100 μ s	5
	P18 x 100 μ s	4
	P19 x 100 μ s	3
30	P20 x 100 μ s	2

The regime described above is shown pictorially in Figure 3.

EXAMPLE 4

TREATMENT OF HIP INJURY

35

The hip is a complex joint subject to stresses primarily in the vertical plane. The hip is subject to both degeneration

- 20 -

as well as trauma including connective tissues and articular surfaces. In order to provide the healthiest physiology to encourage rapid repair and reductions in inflammation, electrobiomimetic stimulus was applied as follows:

5	Period 1 Duration	8 minutes
	Period 2 Duration	12 minutes
	Period 3 Duration	10 minutes
	Period 1 Interval	35 ms
	Period 2 Interval	5 ms
10	Period 3 Interval	50 ms
	Pulse Duration	220 μ s
	P1 x 100 μ s	200
	P2 x 100 μ s	200
	P3 x 100 μ s	200
15	P4 x 100 μ s	200
	P5 x 100 μ s	200
	P6 x 100 μ s	200
	P7 x 100 μ s	180
	P8 x 100 μ s	160
20	P9 x 100 μ s	140
	P10 x 100 μ s	120
	P11 x 100 μ s	100
	P12 x 100 μ s	80
	P13 x 100 μ s	60
25	P14 x 100 μ s	40
	P15 x 100 μ s	20
	P16 x 100 μ s	10
	P17 x 100 μ s	0
	P18 x 100 μ s	0
30	P19 x 100 μ s	0
	P20 x 100 μ s	0

The regime described above is shown pictorially in Figure 4.

35 EXAMPLE 5 TREATMENT OF KNEE INJURY

The knee is subject to multiple injuries which can often be

made more severe by degeneration, pain and loss of mobility. In order to provide the healthiest physiology to encourage rapid repair and reductions in inflammation, electrobiomimetic stimulus was applied as follows:

5	Period 1 Duration	2 minutes
	Period 2 Duration	18 minutes
	Period 3 Duration	10 minutes
	Period 1 Interval	200 ms
10	Period 2 Interval	80 ms
	Period 3 Interval	250 ms
	Pulse Duration	200 μ s
	P1 x 100 μ s	255
	P2 x 100 μ s	240
15	P3 x 100 μ s	220
	P4 x 100 μ s	200
	P5 x 100 μ s	180
	P6 x 100 μ s	100
	P7 x 100 μ s	50
20	P8 x 100 μ s	20
	P9 x 100 μ s	10
	P10 x 100 μ s	5
	P11 x 100 μ s	1
	P12 x 100 μ s	5
25	P13 x 100 μ s	20
	P14 x 100 μ s	50
	P15 x 100 μ s	80
	P16 x 100 μ s	100
	P17 x 100 μ s	150
30	P18 x 100 μ s	200
	P19 x 100 μ s	210
	P20 x 100 μ s	220

The regime described above is shown pictorially in Figure 5.

EXAMPLE 6TREATMENT OF LOWER BACK STRAIN

The lower back is subject to both acute and chronic
 5 conditions involving overuse injury, trauma and degenerative
 conditions. In order to provide the healthiest physiology
 to encourage rapid repair and reductions in inflammation,
 electrobiomimetic stimulus was applied as follows:

10	Period 1 Duration	8 minutes
	Period 2 Duration	12 minutes
	Period 3 Duration	10 minutes
	Period 1 Interval	35 ms
	Period 2 Interval	5 ms
15	Period 3 Interval	50 ms
	Pulse Duration	220µs
	P1 x 100µs	1
	P2 x 100µs	10
	P3 x 100µs	20
20	P4 x 100µs	40
	P5 x 100µs	80
	P6 x 100µs	120
	P7 x 100µs	160
	P8 x 100µs	200
25	P9 x 100µs	220
	P10 x 100µs	240
	P11 x 100µs	255
	P12 x 100µs	240
	P13 x 100µs	220
30	P14 x 100µs	200
	P15 x 100µs	160
	P16 x 100µs	0
	P17 x 100µs	0
	P18 x 100µs	0
35	P19 x 100µs	0
	P20 x 100µs	0

The regime described above is shown pictorially in Figure 6.

EXAMPLE 7TREATMENT OF MID BACK STRAIN

5 The Mid Back region is subject to connective tissue degeneration as well as postural overuse conditions that are often chronic in nature. In order to provide the healthiest physiology to encourage rapid repair and reductions in inflammation, electrobiomimetic stimulus was applied as
10 follows:

	Period 1 Duration	9 minutes
	Period 2 Duration	15 minutes
	Period 3 Duration	6 minutes
15	Period 1 Interval	70 ms
	Period 2 Interval	5 ms
	Period 3 Interval	50 ms
	Pulse Duration	380µs
	P1 x 100µs	4
20	P2 x 100µs	4
	P3 x 100µs	4
	P4 x 100µs	4
	P5 x 100µs	4
	P6 x 100µs	4
25	P7 x 100µs	20
	P8 x 100µs	40
	P9 x 100µs	80
	P10 x 100µs	100
	P11 x 100µs	120
30	P12 x 100µs	180
	P13 x 100µs	200
	P14 x 100µs	220
	P15 x 100µs	0
	P16 x 100µs	0
35	P17 x 100µs	0
	P18 x 100µs	0
	P19 x 100µs	0

P20 x 100µs 0

The regime described above is shown pictorially in Figure 7.

5 EXAMPLE 8 TREATMENT OF NECK STRAIN

The neck is a complex organ that is subject to overuse and traumatic conditions involving a range of musculo-tendinous insertions as well as tendo-osseous insertion point disorders. Degeneration and trauma to the articular surfaces can also play a role in Neck pathologies. In order to provide the healthiest physiology to encourage rapid repair and reductions in inflammation, electrobiomimetic stimulus was applied as follows:

15	Period 1 Duration	8 minutes
	Period 2 Duration	12 minutes
	Period 3 Duration	10 minutes
	Period 1 Interval	40 ms
20	Period 2 Interval	25 ms
	Period 3 Interval	50 ms
	Pulse Duration	220µs
	P1 x 100µs	200
	P2 x 100µs	200
25	P3 x 100µs	200
	P4 x 100µs	200
	P5 x 100µs	200
	P6 x 100µs	200
	P7 x 100µs	200
30	P8 x 100µs	20
	P9 x 100µs	40
	P10 x 100µs	100
	P11 x 100µs	120
	P12 x 100µs	180
35	P13 x 100µs	200
	P14 x 100µs	220
	P15 x 100µs	240

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	P16 x 100μs	0
	P17 x 100μs	0
	P18 x 100μs	0
	P19 x 100μs	0
5	P20 x 100μs	0

The regime described above is shown pictorially in Figure 8.

EXAMPLE 9 TREATMENT OF OSTEOARTHRITIS

10

Osteoarthritis is a degenerative disease that may affect any number of joints or regions of the body. The underling pathology usually involves the loss of articular surface due to a loss of balance between matrix formation and
 15 degeneration. In order to provide the healthiest physiology to encourage rapid repair and reductions in inflammation, electrobiomimetic stimulus was applied as follows:

	Period 1 Duration	5 minutes
20	Period 2 Duration	15 minutes
	Period 3 Duration	10 minutes
	Period 1 Interval	40 ms
	Period 2 Interval	20 ms
	Period 3 Interval	50 ms
25	Pulse Duration	200μs
	P1 x 100μs	50
	P2 x 100μs	25
	P3 x 100μs	3
	P4 x 100μs	3
30	P5 x 100μs	3
	P6 x 100μs	3
	P7 x 100μs	3
	P8 x 100μs	3
	P9 x 100μs	3
35	P10 x 100μs	3
	P11 x 100μs	3
	P12 x 100μs	3

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	P13 x 100µs	3
	P14 x 100µs	3
	P15 x 100µs	3
	P16 x 100µs	0
5	P17 x 100µs	0
	P18 x 100µs	0
	P19 x 100µs	0
	P20 x 100µs	0

10 The regime described above is shown pictorially in Figure 9.

EXAMPLE 10TREATMENT OF SHOULDER INJURY

15 The shoulder often presents with chronic overuse syndromes, which can limit range of motion and dramatically reduce quality of life. The shoulder is subject to overuse and traumatic conditions involving a range of musculo-tendinus insertions as well as tendo-osseous insertion point disorders and can also involve osteoporosis and other bone
 20 related syndromes. In order to provide the healthiest physiology to encourage rapid repair and reductions in inflammation, electrobiomimetic stimulus was applied as follows:

25	Period 1 Duration	8 minutes
	Period 2 Duration	12 minutes
	Period 3 Duration	10 minutes
	Period 1 Interval	35 ms
	Period 2 Interval	5 ms
30	Period 3 Interval	50 ms
	Pulse Duration	200µs
	P1 x 100µs	1
	P2 x 100µs	10
	P3 x 100µs	20
35	P4 x 100µs	40
	P5 x 100µs	80
	P6 x 100µs	120

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	P7 x 100µs	160
	P8 x 100µs	200
	P9 x 100µs	220
	P10 x 100µs	240
5	P11 x 100µs	220
	P12 x 100µs	20
	P13 x 100µs	40
	P14 x 100µs	60
	P15 x 100µs	80
10	P16 x 100µs	100
	P17 x 100µs	0
	P18 x 100µs	0
	P19 x 100µs	0
	P20 x 100µs	0

15

The regime described above is shown pictorially in Figure 10.

EXAMPLE 11 TREATMENT OF VASCULAR DISORDERS

20

Vascular insufficiency disorders are common in chronic musculo-skeletal conditions and can impact in the ability of the condition to resolve fully in the absence of a supporting capillary arcade. Vascular stimulation involving induced electro-osteogenesis can be particularly beneficial in such cases. In order to provide the healthiest physiology to encourage rapid repair and reductions in inflammation, electrobiomimetic stimulus was applied as follows:

30

	Period 1 Duration	5 minutes
	Period 2 Duration	15 minutes
	Period 3 Duration	10 minutes
	Period 1 Interval	14ms
35	Period 2 Interval	10 ms
	Period 3 Interval	20 ms
	Pulse Duration	380µs

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	P1 x 100µs	4
	P2 x 100µs	0
	P3 x 100µs	0
	P4 x 100µs	0
5	P5 x 100µs	0
	P6 x 100µs	0
	P7 x 100µs	0
	P8 x 100µs	0
	P9 x 100µs	0
10	P10 x 100µs	0
	P11 x 100µs	0
	P12 x 100µs	0
	P13 x 100µs	0
	P14 x 100µs	0
15	P15 x 100µs	0
	P16 x 100µs	0
	P17 x 100µs	0
	P18 x 100µs	0
	P19 x 100µs	0
20	P20 x 100µs	0

The regime described above is shown pictorially in Figure 11.

25 EXAMPLE 12 TREATMENT OF WRIST INJURY

The wrist is highly mobile joint subject to many traumatic events and damaging influences. The wrist commonly presents with overuse and articular surface damage as well as bone
 30 and rheumatoid disorders. In order to provide the healthiest physiology to encourage rapid repair and reductions in inflammation, electrobiomimetic stimulus was applied as follows:

35	Period 1 Duration	8 minutes
	Period 2 Duration	12 minutes
	Period 3 Duration	10 minutes

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	Period 1 Interval	35ms
	Period 2 Interval	5 ms
	Period 3 Interval	50 ms
	Pulse Duration	220µs
5	P1 x 100µs	200
	P2 x 100µs	200
	P3 x 100µs	200
	P4 x 100µs	200
	P5 x 100µs	10
10	P6 x 100µs	20
	P7 x 100µs	40
	P8 x 100µs	80
	P9 x 100µs	120
	P10 x 100µs	140
15	P11 x 100µs	160
	P12 x 100µs	200
	P13 x 100µs	220
	P14 x 100µs	0
	P15 x 100µs	0
20	P16 x 100µs	0
	P17 x 100µs	0
	P18 x 100µs	0
	P19 x 100µs	0
	P20 x 100µs	0
25		

The regime described above is shown pictorially in Figure 12.

Claims

1. A method for stimulating cells and tissue *in vivo* comprising the step of applying to said cells and tissue
5 an electrobiomimetic stimulus, wherein the growth characteristics of said cells and tissue are enhanced as compared to cells and tissue not receiving said stimulus.
2. A method according to claim 1, wherein the
10 electrobiomimetic stimulus comprises a pattern of specifically configured time varying EMFP responsible for the enhanced growth characteristics.
3. A method for stimulating cells and tissue *in vivo*
15 comprising the step of applying to said cells and tissue an electrobiomimetic stimulus comprising a plurality of time periods, wherein each time period comprises a plurality of electromagnetic field pulse blocks separated by intervals of no electromagnetic field pulses, each
20 electromagnetic field pulse block comprises a plurality of electromagnetic field pulses of defined duration, wherein each electromagnetic field pulse of the plurality of electromagnetic field pulses is separated by a time variable pulse space and wherein said intervals vary in
25 length of time between each period and wherein the duration of the electromagnetic pulses are uniform.
4. A method according to claim 3, wherein the
30 electrobiomimetic stimulus comprises between 2 and 4 time periods, wherein each time period comprises blocks of electromagnetic field pulse, which are distinct from each other..
5. A method according to claim 3, wherein the
35 electrobiomimetic stimulus comprises between 2 and 3 time periods, wherein each time period comprises blocks of electromagnetic field pulse, which are distinct from each

other..

6. A method according to claim 3, wherein the electrobiomimetic stimulus comprises 3 time periods, wherein
5 each time period comprises blocks of electromagnetic field pulse, which are distinct from each other.

7. A method according to any one of claims 3 to 6, wherein the time periods simulating a gentle walk, explosive
10 exercise and then light jog, wherein the rate or frequency of delivery of the blocks of electromagnetic field pulse varies.

8. A method according to claim 3, wherein the
15 electrobiomimetic stimulus comprises 3 time periods, wherein time period 1 has duration of between 2 minutes and 9 minutes, time period 2 has duration between 10 minutes and 18 minutes and time period 3 has duration between 6 minutes and 12 minutes.

20

9. A method according to any one of claims 3 to 8, wherein each electromagnetic field pulse block is separated by an interval of no electromagnetic field pulse.

25 10. A method according to claim 9, wherein the interval separating the electromagnetic field pulse blocks has variable time lengths.

11. A method according to claim 9, wherein the
30 interval between each electromagnetic field pulse block in period 1 will be between 14ms and 200ms, while the interval in period 2 will be between 5ms and 80ms and the interval in period 3 between 20ms and 100ms.

35 12. A method according to any one of claims 3 to 11, wherein the magnetic field intensity used is between 1 Gauss to 100 Gauss.

13. A method according to claim 12, wherein the magnetic field intensity is between about 1 Gauss to 100 Gauss.

5

14. A method according to claim 12, wherein the magnetic field intensity is about 3 Gauss.

15. A method according to any one of claims 3 to 14,
10 wherein the pulse duration is between 200 μ s and 380 μ s.

16. A method according to any one of claims 3 to 15, comprising a plurality of electromagnetic field pulses.

15 17. A method according to claim 16, wherein the number of electromagnetic field pulses in each block is between 1 and 50.

18. A method according to claim 16, wherein the
20 number of electromagnetic field pulses in each block is between 10 and 30.

19. A method according to claim 16, wherein the number of electromagnetic field pulses in each block is
25 about 20.

20. A method according to any one of claims 3 to 19, wherein the electromagnetic field pulse within each block is spaced by varying time spaces.

30

21. A method according to claim 20, wherein the time space between each electromagnetic field pulse is between 0 and 300000 μ s.

35 22. A method for treating tissue *in situ* comprising:
(i) collecting a selected portion of tissue,
and

(ii) securing said portion of tissue adjacent to an energy transmitting element; transmitting an electrobiomimetic stimulus from said energy transmitting element; and transmitting said electrobiomimetic stimulus to target cells within said portion of tissue until growth characteristics of said cells and tissue are altered as compared to cells and tissue not receiving said stimulus.

23. A system to treat tissue *in vivo*, the system comprising: an energy source; an energy transmitting element for providing an electrobiomimetic stimulus; and a holding mechanism adapted to hold tissue, such that electrobiomimetic stimulus emitted by said energy transmitting element treats said tissue.

24. A method of treating an individual comprising the steps of:

- (i) providing a device comprising an electromagnetic field pulse generator;
- (ii) positioning the device adjacent to a bodily tissue of an individual; and
- (iii) operating the device for a duration, at a frequency, and at a peak effective to elicit a therapeutic response in the individual, wherein the device is positioned relative to the individual such that the device induces an electrobiomimetic stimulus within the bodily tissue.

25. A method according to claim 24, wherein the individual has a bone, joint, soft-tissue, or connective tissue disorder and the therapeutic response comprises a reduction or elimination of inflammation and/or pain in a bone, joint, soft-tissue, or connective tissue of the individual.

26. A method according to claim 25, wherein the individual has a disorder selected from the group

consisting of adhesive capsulitis, tennis elbow,
osteoarthritis, back pain, multiple sclerosis, tendon
inflammation, and carpal tunnel syndrome, and the
therapeutic response comprises a reduction or elimination
5 of inflammation and/or pain associated with the disorder

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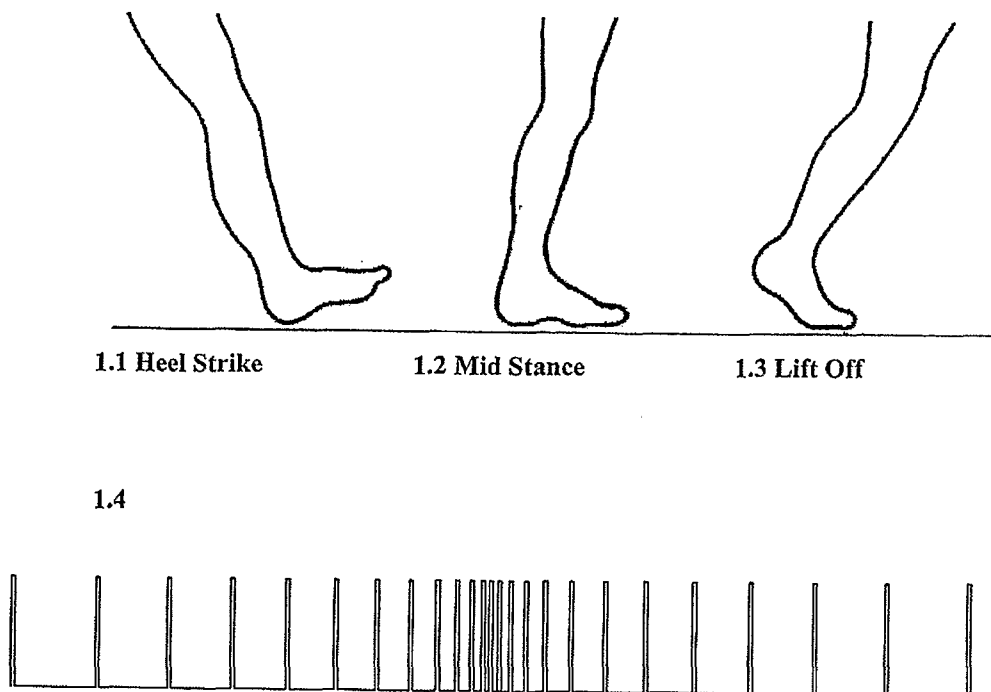


FIGURE 1

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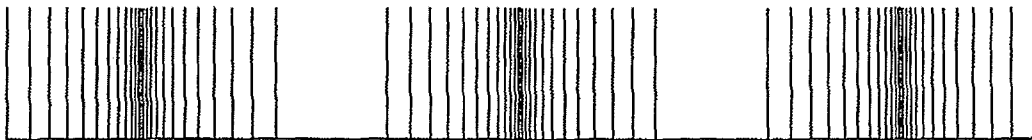
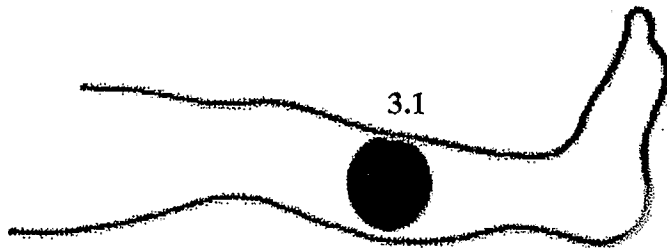
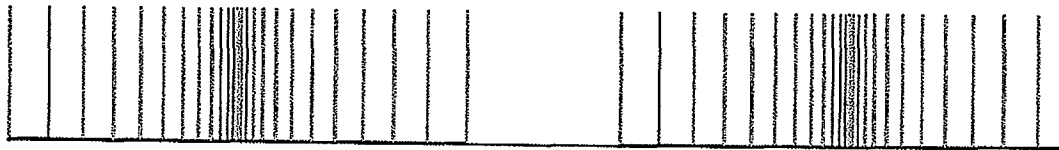
2.1 Walk – $1.5 \times \text{BW}$ - 1.0 Cycles per second2.2 Jog – $2.0 \times \text{BW}$ - 1.8 Cycles per second2.3 Run – $3.5 \times \text{BW}$ - 2.3 Cycles per second

FIGURE 2

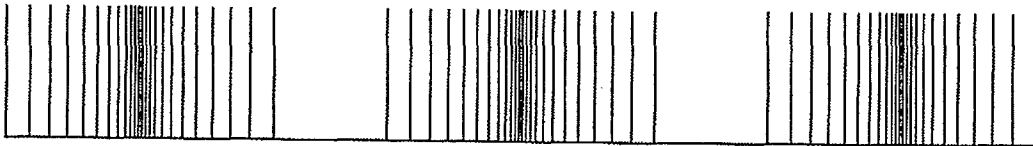
3/15



3.2



3.3



3.4

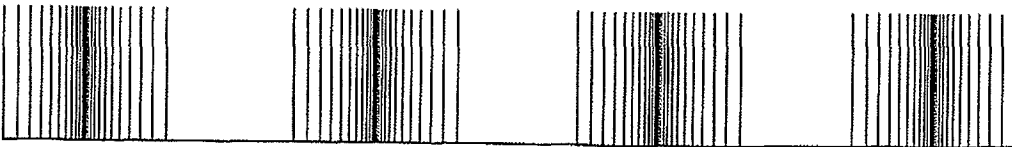


FIGURE 3

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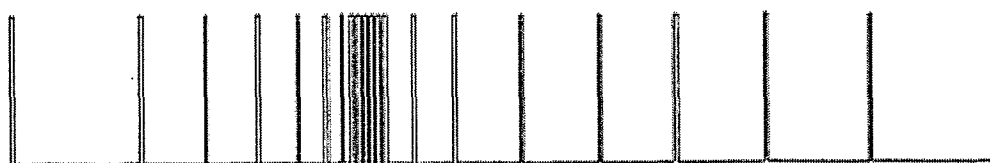


FIGURE 4

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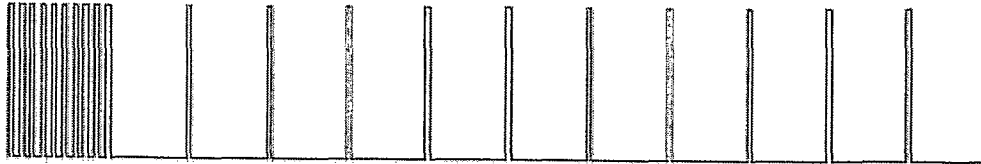


FIGURE 5

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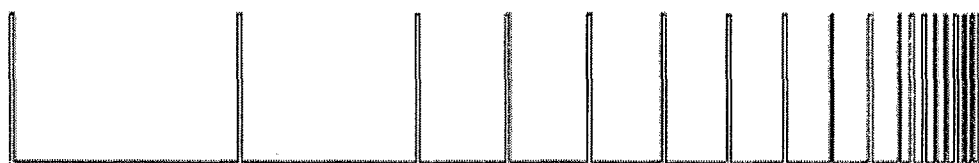


FIGURE 6

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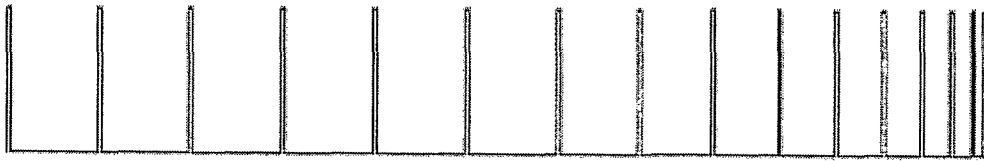


FIGURE 7

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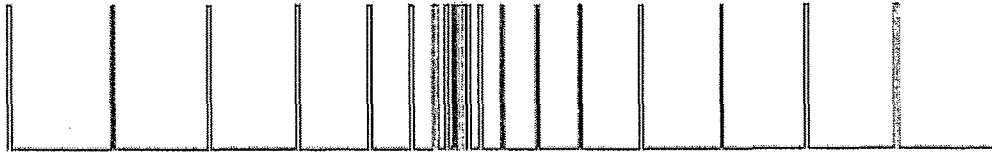


FIGURE 8

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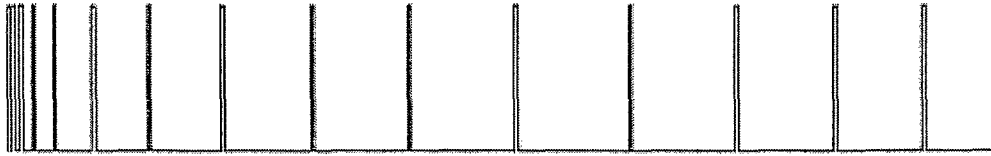


FIGURE 9

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FIGURE 10

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FIGURE 11

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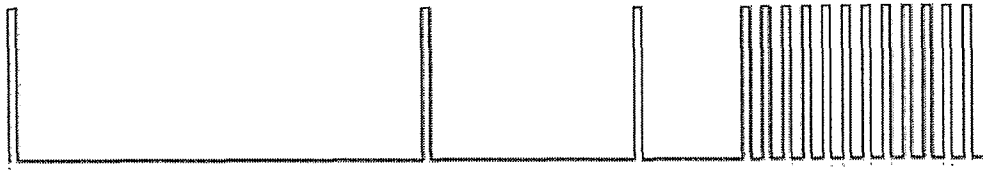


FIGURE 12

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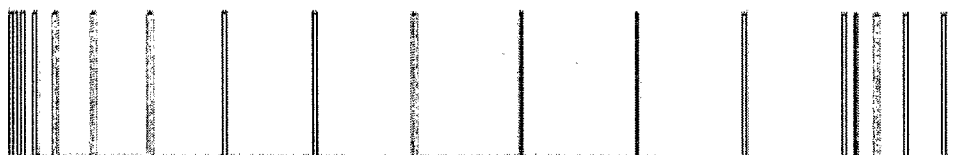


FIGURE 13

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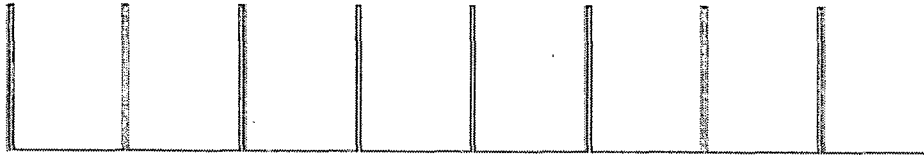


FIGURE 14

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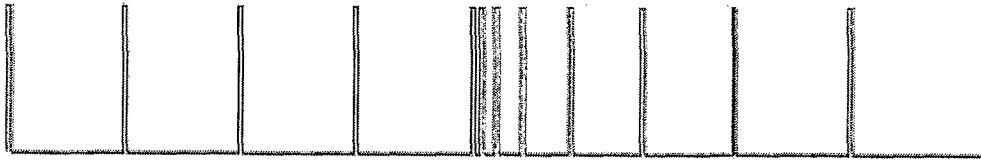


FIGURE 15

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2007/000454

A. CLASSIFICATION OF SUBJECT MATTER												
Int. Cl. <i>A61N 1/36</i> (2006.01)												
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 data base and, where practicable, search terms used)												
DWPI (IPC: A61N ; KEYWORDS: electro+, bioelect+, +biomim+, stimulat+, grow+, regen+, imitat+, simulat+, mimic+, replicat+, movement+, exercis+, action+, walk+, jog+, run+, puls+)												
C. DOCUMENTS CONSIDERED TO BE RELEVANT												
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.										
X	Derwent Abstract Accession No. A3701A/02, Class P34, SU 554870 A (RIGA TRAUMATOLOGY) 23 May 1977 See whole English language abstract.	1 to 26										
A	Derwent Abstract Accession No. 84-105311/17, Class P34, SU 865299 A (MIKHAILICHENKO) 25 September 1981 See whole English language abstract.											
A	US 4922908 A (MORAWETZ et al.) 8 May 1990 See in particular figure 9.											
☒ Further documents are listed in the continuation of Box C ☒ See patent family annex												
* Special categories of cited documents: <table border="0"> <tr> <td>"A" document defining the general state of the art which is not considered to be of particular relevance</td> <td>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td> </tr> <tr> <td>"E" earlier application or patent but published on or after the international filing date</td> <td>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td> </tr> <tr> <td>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td> <td>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td> </tr> <tr> <td>"O" document referring to an oral disclosure, use, exhibition or other means</td> <td>"&" document member of the same patent family</td> </tr> <tr> <td>"P" document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </table>			"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	"P" document published prior to the international filing date but later than the priority date claimed	
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"P" document published prior to the international filing date but later than the priority date claimed												
Date of the actual completion of the international search 20 June 2007		Date of mailing of the international search report 3 - JUL 2007										
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929		Authorized officer PETER T. WEST AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No : (02) 6283 2108										

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2007/000454

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4620543 A (HEPPENSTALL et al.) 4 November 1986 See whole document.	
A	US 4338945 A (KOSUGI et al.) 13 July 1982 See in particular figure 2.	
A	US 4326534 A (AXELGAARD et al.) 27 April 1982 See in particular figure 4.	
A	US 4105017 A (RYABY et al.) 8 August 1978 See in particular item 36.	
A	US 3983881 A (WICKHAM) 5 October 1976 See in particular figure 3a.	
A	US 3794022 A (NAWRACAJ et al.) 26 February 1974 See whole document.	

Information on patent family members

PCT/AU2007/000454

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.

Patent Document Cited in Search Report			Patent Family Member				
SU	554870	NONE					
SU	865299	NONE					
US	4922908	US	4887603				
US	4620543	NONE					
US	4338945	JP	54119792				
US	4326534	NONE					
US	4105017	AT	788977	AU	30738/77	BE	860745
		BG	30919	BR	7707629	CA	1092196
		CH	621942	DE	2748780	DK	508177
		EP	0042889	ES	464178	ES	473758
		FR	2371205	GB	1596512	GB	1596513
		HK	21682	HK	21782	IL	53346
		JP	53063791	LU	78533	MC	1191
		MX	147342	NL	7712694	NL	8503057
		NO	773925	PH	13304	PL	202175
		SE	7712939	US	4266532	US	4266533
	US	4315503					
US	3983881	AU	14196/76	CA	1069182	GB	1543178
US	3794022	NONE					
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.							
END OF ANNEX							