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Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2009/117573 A1

(54) Title: MOVING A SMALL OBJECT IN A DIRECTION

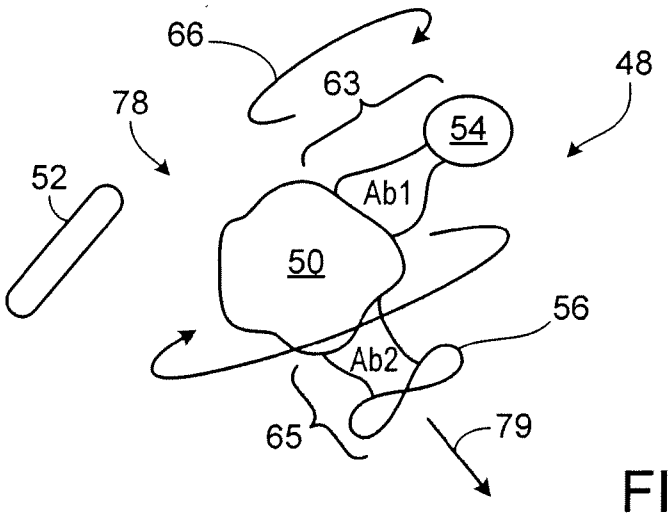

FIG. 4

(57) Abstract: For directional motion of a small object, a combination of at least two different properties is imparted to the object. At least one of the properties being responsive to an external influence to produce a force or torque acting on the object. At least another of the properties is responsive to the force or torque to cause a directional motion of the object.

Moving a Small Object in a Direction

Background

This application has the benefit of the filing date of United States provisional application 61/038,573, filed March 21, 2008, and incorporated in its entirety here by reference.

United States patent application 12/103,281, filed April 15, 2008, is incorporated in its entirety here by reference.

United States provisional application 60/987,674, filed November 13, 2007, is incorporated in its entirety here by reference.

This description relates to moving a small object in a direction.

Small objects can be moved in specific directions by applying an external force or torque.

In some cases, the external force acts on a property of the object that is inherent to the object, renders the object susceptible to the force, and differs from a property of the medium in which the object is to be moved. For example, as shown in figure 1, in dielectrophoresis, an oscillating electric field (the external force 10) is applied to a cell (the object 12). The cell has a value of dielectric constant (a property 14) that is natural (inherent to the cell), makes the cell susceptible to the force, and is different from the value of dielectric constant of the fluid (the medium 16) around it.

In some cases, a property 18 that makes an object susceptible to an external force is not inherent to the object, but instead is imparted to it. For example, a charge (the property) can be imparted to a denatured protein by attaching negatively charged SDS molecules to it. Electrophoresis can then be performed by applying an electric field.

In some cases, for example a chiral molecule 20 as shown in figure 2, the object can be moved in a direction 22 by applying a rotating electric field 24 (the external influence). The rotating field acts on an electric dipole moment 26 of the molecule (the dipole moment being a first inherent property of the chiral molecule), causing the molecule to rotate. The chirality 28 of the molecule (its chirality being a second, inherent property)

translates the molecule's rotation 30 into motion in a direction 22. The direction 22 depends on the molecule's handedness (i.e., its chirality).

Summary

In general, in an aspect, for directional motion of a small object, a combination of at least two different properties is imparted to the object, at least one of the properties being responsiveness to an external influence to produce a force or torque acting on the object, at least another of the properties being responsiveness to the force or torque to cause a directional motion of the object.

Implementations may include one or more of the following features. Prior to the combination of the at least two properties being imparted to the object, no directional motion of the object is produced in response to the external influence. Prior to the combination of the at least two properties being imparted to the object, any directional motion of the object in response to the external influence is less than after the imparting. Neither of the properties is inherent in the object.

The object includes a cell, for example, a cell that is abnormal, dead, diseased, or drugged or exposed to other chemicals. The object includes a virus. The object includes, for example, a bacterium, a molecule, a biomolecule, a protein (which has, for example, a post-translational modification), a peptide, an enzyme, a DNA or RNA molecule, which may include an epimer, a polymer, a bead, a nanoparticle, an organelle, a liposome, a vesicle, a biomolecular aggregate, a molecular aggregate, or a spore.

The imparting includes attaching at least one other object, such as an antibody. The imparting includes adding another object. The other object includes a transfected gene. The imparting includes removing a part of the object. The imparting includes causing a reaction on the object. The reaction, for example, is molecular, cellular, or chemical.

The external influence includes a force field, such as electric, magnetic, or gravitational. The gravitational field is centrifugal. The field includes a pressure field or an acoustic field. The force field is static, oscillating, or rotating. The external influence includes a reaction. The reaction is chemical, such as rotatory, molecular, or cellular. The external

influence includes a kinetic force, such as electroosmotic, electrophoretic, or one based on dielectrophoretic, optophoretic, or thermophoretic. The external influence includes a gradient, such as a chemical gradient or a field gradient. The other property includes chirality.

One of the properties may be imparted in the form of a dipole, such as an electric dipole or a magnetic dipole. The external influence may be a rotating electric field or a rotating magnetic field.

These and other aspects and features, and combinations of them, may be expressed as methods, apparatus, systems, means for performing functions, program products, and in other ways.

Other advantages and features will become apparent from the following description and from the claims.

Description

Figures 1, 2, 3, and 4 are schematic views of objects and external influences.

As shown in figure 3, a small object 40 can be moved in a direction 42 by (for example) an external force or torque 44 that operates on the object by means of at least two properties of the object (at least two of which 46, 48 are not inherent but have been imparted to the object). The motion in direction 42 occurs only if the object has both of the imparted properties, like an AND-logic gate, the output of which is 1 (corresponding to directional motion) only if the two inputs (the imparted properties), both have a value 1 (i.e., are present). There can be more than two imparted properties, and the object can also have one or more inherent properties.

For example, as shown in figure 3, assume that a biological sample 48 includes two different types of cells, one population of target cells 50 (TC's) and a second population of non-target cells 52 (NTC's), and the goal is to obtain an enriched population of TC's by moving 49 TC's from the sample and leaving NTC's behind.

As shown in figure 4, assume that we have supplies of (a) two antibodies (Ab1 and Ab2) that both have a stronger affinity to TC's than to NTC's, e.g., they preferentially bind to TC's and much less so to NTC's, (b) magnetic beads 54 that are super-paramagnetic, i.e., they exhibit magnetism (or they acquire a magnetic dipole moment) in the presence of a magnetic field, and (c) small objects 56 (e.g., ~1-10μm diameter, or .1-1μm diameter), either manufactured or natural that have a certain chirality (i.e., right-handed or left-handed, so let's assume all left-handed in this case). We sometimes call the small objects 56 propellers.

As shown in figure 4, we attach each Ab1 to a magnetic bead to form one complex 63, and each Ab2 to an artificial propeller 56 to form a complex 65, and we put both complexes (either sequentially or simultaneously) into the sample 48 that contains both TC's and NTC's. (In figure 4, we have only shown a single TC and a single NTC. Each Ab1-magnetic bead complex 63 will attach to a TC in a specific manner with a relatively higher probability or to an NTC in a non-specific manner with a relatively lower probability. For simplicity of discussion, assume that the Ab1-magnetic bead complexes will only bind to TC's and that the non-specific binding to NTC's is negligible.

Similarly, assume for simplicity that the Ab2-propeller complex 65 binds only to TC's (and not to NTC's).

When an Ab1-magnetic bead complex binds to a TC, the magnetic bead will impart a magnetic dipole to the TC; an Ab2-propeller complex, in turn, will impart chirality to the TC.

We then apply a rotating magnetic field 66 to the sample, causing all magnetic beads, whether bound to TC's or not, to rotate with the magnetic field.

Any magnetic bead that is not bound to a cell or any complex of a bead bound to a cell that does not also have a propeller bound to it will not have any chirality, and therefore, will not move in a particular direction, in other words, it will not experience any directional motion.

Conversely, a propeller that is not bound to a cell or any complex of a propeller that is bound to a cell that does not also have a magnetic bead bound to it, will not have any magnetism, and the rotating magnetic field will have no effect on it. Even though the complex has chirality, it lacks magnetism to convert the external influence (the rotating magnetic field, in this case) into a force or a torque to cause it to rotate (and in turn be moved in a direction).

Only a cell 78 that has both a magnetic bead and a propeller attached to it (using Ab1 and Ab2, respectively, in this example) will rotate in response to a rotating magnetic field, and move in a direction 79 as the rotation is converted into directional motion (as a result of the chirality imparted to the cell by the propeller). Additional information about the use of rotation and chirality for propeller motion can be found in United States patent application 12/103,281, filed April 15, 2008, and incorporated in its entirety here by reference.

By imparting two properties, e.g., magnetism and chirality, that are not inherent to a small object (e.g., a cell), e.g. by attaching two other objects (one with magnetism, the other with chirality), an external influence (e.g., a rotating magnetic field) can be converted into a torque on the cell to rotate it and the rotation be used to move the cell in a particular direction (that is determined by the handedness of the propeller). In this example, both magnetism and chirality are required to generate the directional motion; if one is missing, there's none (without magnetism, the cell does not rotate, and without chirality, it is not propelled).

Using this combination of properties and an external influence, for example, target cells can propel themselves to a specific location in the container (using the specific binding of antibodies appropriate for those cells), leaving the non-target cells behind. Because both antibodies are selected to be ones that bind to the target cell and not to the non-target cell, the enrichment factor can be greatly enhanced. Furthermore, losses due to harsh and the use of possibly multiple extraction steps can be avoided, and the yield of such an enrichment process can be high. Yield loss due to de-bulking, for example, can be reduced.

Other examples are also within the scope of the claims.

The object need not be a cell. It could be a virus, bacteria, molecule, biomolecule, protein, peptide, enzyme, DNA, RNA, small molecule, polymer, bead, nanoparticle, organelles, liposome, vesicle, biomolecular aggregate, molecular aggregate, or spore, or any other small particle or object.

The cells may be modified to be abnormal, dead, diseased, and/or drugged; the proteins may have certain PTMs (post-translational modifications, e.g., glycosylated, phosphorylated); DNA and/or RNA molecules may be epimers.

The properties can be imparted to the objects in a wide variety of different ways. For example, an object (e.g., an antibody or a transfected gene) can be attached to or added to the target object. A portion of the target object can be removed. A reaction can be caused on the object (e.g., chemical, molecular or cellular) to change one of its properties.

The external influence may be: a field (electric, magnetic, electromagnetic, gravitational/centrifugal, pressure/acoustic/ultrasound), a reaction (e.g. chemical/rotatory chemistry, molecular, cellular), a kinetic force (e.g. electroosmotic, electrophoretic, dielectrophoretic, optophoretic, thermophoretic), or a gradient (e.g. chemical, field).

The property of the object to convert the external influence into a force or torque on the object may be a property that interacts with the external influence. For example, the property may be a permanent or induced electric dipole moment that interacts with an electric field; a permanent or induced magnetic dipole moment that interacts with a magnetic field; permittivity or permeability with respect to an electromagnetic field; mass (or buoyancy) with respect to a gravitational field; and so on for other external influences, including the ones mentioned above.

The second property to convert the force or torque on the object into directional motion of the object may be chirality, as explained in the examples, or other properties that produce directional motion.

We have used the word inherent to refer, for example, to a property that exists in an object in its naturally occurring form, or in the object in a form in which it is initially manufactured or altered or contemplated.

In some cases, the two properties can be imparted to the target object by a single action or a single other object. For example, the propelling property and the force receiving property can be embodied in a single object which is then attached to the target object.

In some cases, the object may have the two properties and the effect of the two properties for purposes of causing directional is enhanced by imparting the two properties again or in greater amount or in a second version, for example, to the object.

Claims

1. A method for use in directional motion of a small object, the method comprising,

imparting to the object a combination of at least two different properties,

at least one of the properties being responsive to an external influence to produce a force or torque acting on the object,

at least another of the properties being responsive to the force or torque to enhance the directional motion of the object.

2. The method of claim 1 in which, prior to the combination of the at least two properties being imparted to the object, there is no directional motion of the object in response to the external influence.

3. The method of claim1 in which, prior to the combination of the at least two properties being imparted to the object, the directional motion of the object in response to the external influence is less than after the imparting.

4. The method of claim 1 in which neither of the properties is inherent in the object.

5. The method of claim 1 in which the object comprises a cell.

6. The method of claim 5 in which the cell is abnormal.

7. The method of claim 5 in which the cell is dead.

8. The method of claim 5 in which the cell is diseased.

9. The method of claim 5 in which the cell is drugged or exposed to other chemicals.

10. The method of claim 1 in which the object comprises a virus.

11. The method of claim 1 in which the object comprises a bacterium.

12. The method of claim 1 in which the object comprises a molecule.

13. The method of claim 1 in which the object comprises a biomolecule.

14. The method of claim 1 in which the object comprises a protein.

15. The method of claim 14 in which the protein has a post-translational modification.

16. The method of claim 1 in which the object comprises a peptide.

17. The method of claim 1 in which the object comprises an enzyme.

18. The method of claim 1 in which the object comprises a DNA molecule.

19. The method of claim 18 in which the DNA molecule comprises an epimer.

20. The method of claim 1 in which the object comprises an RNA molecule.

21. The method of claim 20 in which the RNA molecule comprises an epimer.

22. The method of claim 1 in which the object comprises a polymer.

23. The method of claim 1 in which the object comprises a bead.

24. The method of claim 1 in which the object comprises a nanoparticle.

25. The method of claim 1 in which the object comprises an organelle.

26. The method of claim 1 in which the object comprises a liposome.

27. The method of claim 1 in which the object is a vesicle.

28. The method of claim 1 in which the object comprises a biomolecular aggregate.

29. The method of claim 1 in which the object comprises a molecular aggregate.

30. The method of claim 1 in which the object comprises a spore.

31. The method of claim 1 in which the imparting comprises attaching at least one other object.

32. The method of claim 31 in which the other object comprises an antibody.

33. The method of claim 1 in which the imparting comprises adding another object.

34. The method of claim 33 in which the other object comprises a transfected gene.

35. The method of claim 1 in which the imparting comprises removing a part of the object.

36. The method of claim 1 in which the imparting comprises causing a reaction on the object.

37. The method of claim 36 in which the reaction is molecular.

38. The method of claim 36 in which the reaction is cellular.

39. The method of claim 36 in which the reaction is chemical.

40. The method of claim 1 in which the external influence comprises a force field.

41. The method of claim 40 in which the force field is static.

42. The method of claim 40 in which the force field is oscillating.

43. The method of claim 40 in which the force field is rotating.

44. The method of claim 40 in which the field comprises an electric field.

45. The method of claim 40 in which the field comprises a magnetic field.

46. The method of claim 40 in which the field comprises a gravitational field.

47. The method of claim 46 in which the gravitational field is centrifugal.

48. The method of claim 40 in which the field comprises a pressure field.

49. The method of claim 40 in which the field comprises an acoustic field.

50. The method of claim 1 in which the external influence comprises a reaction.

51. The method of claim 50 in which the reaction is chemical.

52. The method of claim 51 in which the chemical reaction is rotatory.

53. The method of claim 50 in which the reaction is molecular.

54. The method of claim 50 in which the reaction is cellular.

55. The method of claim 1 in which the external influence comprises a kinetic force.

56. The method of claim 55 in which the kinetic force is electroosmotic.

57. The method of claim 55 in which the kinetic force is based on electrophoretic.

58. The method of claim 55 in which the kinetic force is based on dielectrophoretic.

59. The method of claim 55 in which the kinetic force is based on optophoretic.

60. The method of claim 55 in which the kinetic force is based on thermophoretic.

61. The method of claim 1 in which the external influence comprises a gradient.

62. The method of claim 61 in which the gradient comprises a chemical gradient.

63. The method of claim 61 in which the gradient comprises a field gradient.

64. The method of claim 1 in which the other property comprises chirality.

65. The method of claim 1 in which one of the properties is imparted in the form of a dipole.

66. The method of claim 65 in which the dipole comprises an electric dipole.

67. The method of claim 65 in which the dipole comprises a magnetic dipole.

68. The method of claim 66 in which the external influence comprises a rotating electric field.

69. The method of claim 67 in which the external influence comprises a rotating magnetic field.

70. A method comprising

enhancing directional motion of a small object by applying an external influence to produce a force or torque acting on the object by operation of a first property that has been imparted to the object, the force or torque enhancing the directional motion of the

object by operation of a second property that has been imparted to the object and includes responsiveness to the force or torque to cause the directional motion.

71. The method of claim 70 in which the small object is part of a first quantity of such small objects having both the first and second properties, and the quantity is mixed with a second quantity of other small objects that do not have both the first and second properties, and in which directional motion of the objects in the first quantity is enhanced relative to the second quantity of small objects.

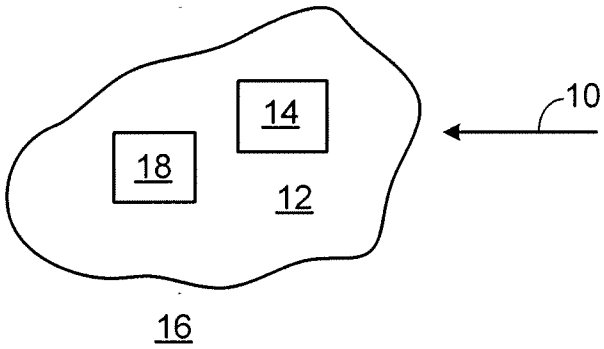

FIG. 1

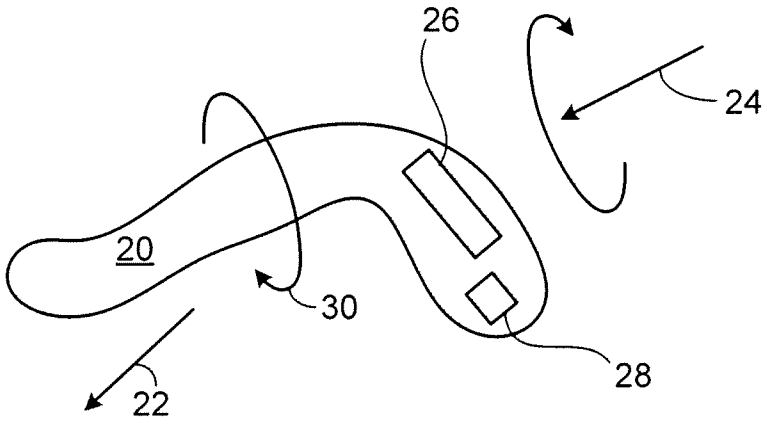

FIG. 2

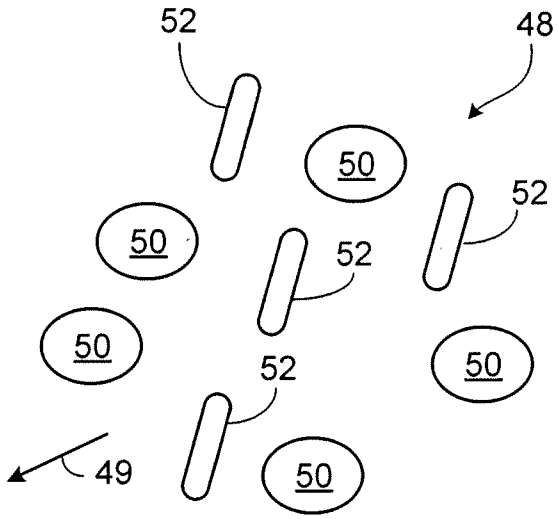
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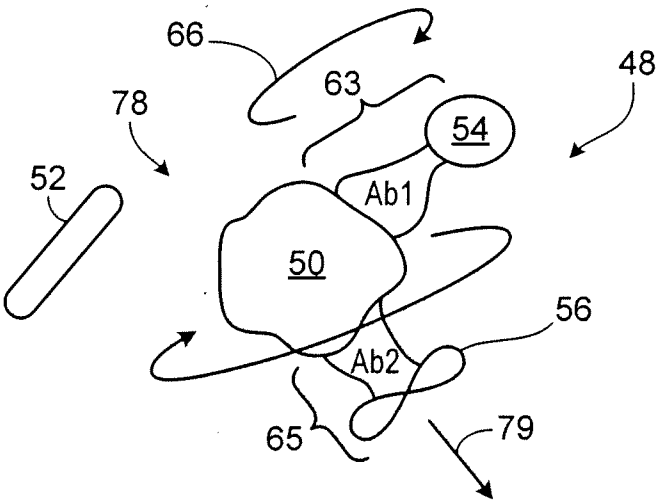
FIG. 3


66
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Ab1
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Ab2
65
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FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/37661

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12N 13/00 (2009.01)
USPC - 435/173.1
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)
USPC - 435/173.1, 173.9

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8) - C12N 13/00; C07C 1/00; B01J 19/09 (2009.01)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (USPT, PGPB, USOC, EPAB, JPAB), Google: osman, kibar, propeller, rotate, oscillate, magnetic, electrical, field, cell, molecule, dipole, virus, chiral

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	FORSTER et al, "Use of Moving Optical Gradient Fields for Analysis of Apoptotic Cellular Responses in a Chronic Myeloid Leukemia Cell Model", Anal. Biochem. 2004 Apr 1;327(1):14-22. Entire document, particularly pg 1-5.	1-9, 40, 41, 61, 63, 70 and 71 --- 10-32, 64
Y	US 5,752,606 A (WILSON et al.) 19 May 1998 (19.05.1998). Col 2, ln 1-9; col 7, ln 11-20.	10-22, 25-29
Y	WO 2007/146675 A2 (KIBAR) 21 December 2007 (21.12.2007). Pg 5, ln 15; pg 7, ln 17-20; pg 17, ln 3-8; pg 24, ln 20-24.	19, 21, 23, 24, 30-32, 64
A	PAREDES et al., Simulated Moving Bed Chromatography: from chiral molecules to biocompounds. Analytica World, 2004.	1-32, 40, 41, 61, 63, 64, 70, 71

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"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)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"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
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 July 2009 (13.07.2009)	21 JUL 2009

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/37661

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

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

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 extra sheet

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

2. ☐ As all searchable claims could be searched without effort justifying 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.:
1-30, 31-32, 40-41, 61, 63-64 and 70-71

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.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/37661

Group I, claims 1-30, 31-32, 40-41, 61, 63-64 and 70-71, directed to a method for use in directional motion of a small object comprising imparting to the object a combination of at least two different properties, wherein imparting comprises attaching at least an antibody to the object, and wherein the external influence to be exerted comprises a static force field.

Group II+, claims 31-32, 42-49, and 55-60 directed to a method for use in directional motion of a small object comprising imparting to the object a combination of at least two different properties, wherein imparting comprises attaching at least an antibody to the object, and wherein the external influence to be exerted comprises one of the following: a) force field: oscillating, rotating, electric, magnetic, centrifugal, pressure, and acoustic; and b) kinetic field: electrophoretic, dielectrophoretic, optophoretic and thermophoretic. If Applicant elects to have this groups searched, Applicant must specify the specific the external influence for search.

Group III+, claims 33-34, 42-49, and 55-60 directed to a method for use in directional motion of a small object comprising imparting to the object a combination of at least two different properties, wherein imparting comprises adding a transfected gene to the object, and wherein the external influence to be exerted comprises one of the following: a) force field: oscillating, rotating, electric, magnetic, centrifugal, pressure, and acoustic; and b) kinetic field: electrophoretic, dielectrophoretic, optophoretic and thermophoretic. If Applicant elects to have this groups searched, Applicant must specify the specific the external influence for search.

Group IV+, claims 35, 42-49, and 55-60 directed to a method for use in directional motion of a small object comprising imparting to the object a combination of at least two different properties, wherein imparting comprises removing a part of the object, , and wherein the external influence to be exerted comprises one of the following: a) force field: oscillating, rotating, electric, magnetic, centrifugal, pressure, and acoustic; and b) kinetic field: electrophoretic, dielectrophoretic, optophoretic and thermophoretic. If Applicant elects to have this groups searched, Applicant must specify the specific the external influence for search.

Group V, claims 36-37, 50, 53 and 62, directed to a method for use in directional motion of a small object comprising imparting to the object a combination of at least two different properties, wherein imparting comprises causing a molecular reaction on the object, and wherein the external influence to be exerted is a molecular reaction.

Group VI, claims 36, 38, 50, 54 and 62 directed to a method for use in directional motion of a small object comprising imparting to the object a combination of at least two different properties, wherein imparting comprises causing a cellular reaction on the object, and wherein the external influence to be exerted is a cellular reaction.

Group VII, claims 36, 39, 50, 51 and 62 directed to a method for use in directional motion of a small object comprising imparting to the object a combination of at least two different properties, wherein imparting comprises causing a chemical reaction on the object, and wherein the external influence to be exerted is a chemical reaction.

Group VIII, claims 36, 50, 52 and 62 directed to a method for use in directional motion of a small object comprising imparting to the object a combination of at least two different properties, wherein imparting comprises causing a reaction on the object, and wherein the external influence to be exerted is a rotary reaction.

Group IX, claims 65-66 and 68, directed to a method for use in directional motion of a small object comprising imparting to the object a combination of at least two different properties, wherein imparting comprises an electric dipole, and wherein the external influence to be exerted is a rotating electric field.

Group X, claims 65, 67 and 69, directed to a method for use in directional motion of a small object comprising imparting to the object a combination of at least two different properties, wherein imparting comprises an magnetic dipole, and wherein the external influence to be exerted is a rotating magnetic field.

Total number of groups: X+

Reason for holding lack of unity: The technical feature shared among the listed groups is a method for use in directional motion of a small object comprising imparting to the object a combination of at least two different properties. This shared technical feature fails to provide a contribution over the prior art, as evidenced by Forster et al. Without a contribution over the prior art, the noted shared technical feature is not a shared special technical feature. In the absence of a shared special technical feature, the inventions lack unity with one another.