METHODS FOR DRUG DELIVERY

CROSS-REFERENCE

This application claims the benefit of priority under 35 U.S.C. section 119(e) to US Provisional Application 61/553,003, filed October 28, 2011; and US Provisional Application 61/680,847, filed August 8, 2012; the contents of which are incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

[0001] Numerous cancer-related therapeutics are under preclinical, phase I or phase II clinical trial and evaluations at any particular time; however, most of them will fail to advance. In fact, numerous drug candidates fail in the preclinical test, and it is estimated that more than 90% of cancer-related therapeutics will fail phase I or II clinical trial evaluation. The failure rate in phase III trials is almost 50%, and the cost of new drug development from discovery through phase Ill trials is between $0.8 billion and $1.7 billion and can take between eight and ten years.

[0002] In addition, many subjects fail to respond even to standard drugs that have been shown to be efficacious. For reasons that are not currently well understood or easily evaluated, individual subjects may not respond to standard drug therapy. One significant challenge in the field of oncology is to exclude treatment selection for individual subjects having cell autonomous resistance to a candidate drug to reduce the risk of unnecessary side effects. A related problem is that excessive systemic concentrations are required for many oncology drug candidates in efforts to achieve a desired concentration at a tumor site, an issue compounded by poor drug penetration in many under-vascularized tumors (Tunggal et al., 1999 *Clin. Canc. Res.* 5:1583).

[0003] The present invention addresses these and similar needs, and offers other related advantages.

SUMMARY OF THE INVENTION

[0004] In one aspect, there is provided a device for delivering one or more agents into a solid tissue comprising: one or more needles arranged in an array, wherein said one or more needles comprise one or more agents, and wherein said one or more agents are delivered to said solid tissue by withdrawing said one or more needles from said solid tissue.

[0004a] In another ~~one~~ aspect, the present disclosure provides a method of delivering a plurality of agents to a solid tissue of a subject, comprising:

(a) inserting a plurality of microdialysis probes to the solid tissue; and

CLAIMS

WHAT IS CLAIMED IS:

1. A method of delivering a plurality of agents to a solid tissue of a subject, comprising:

(a) inserting a plurality of microdialysis probes to said solid tissue; and

(b) delivering said plurality of agents to said solid tissue through said plurality of microdialysis probes.

2. A method of delivering one or more agents to a solid tissue of a subject, comprising:

(a) inserting one or more needles to said solid tissue; and

(b) delivering said one or more agents to said solid tissue by withdrawing said one or more needles from said solid tissue and injecting said one or more agents into said solid tissue.

3. A method of delivering two or more agents to a solid tissue of a subject, comprising: (a) administering at least one of said two or more agents to said subject systemically; and (b) delivering at least one of said two or more agents to said solid tissue with at least one microdialysis probe or at least one needle, wherein said agent(s) administered in (a) is different from said agent(s) delivered in (b).

4. The method of any one of claims 1, 2 or 3, further comprising evaluating an effect of said agent(s) on said solid tissue.

5. The method of claim 1 or 3, wherein at least one of said microdialysis probe(s) when used is Y-shaped.

6. The method of claim 1 or 3, wherein at least one of said microdialysis probe(s) when used is linear.

7. The method of claim 1 or 3, wherein said agents are delivered to said solid tissue by flowing said agents through said microdialysis probe(s).

8. The method of claim 7, wherein the flow rate of said agents is at least about 0.1 μl/min.

9. The method of claim 7, wherein the flow rate of said agents is between about 0.1 μl/min and about 3 μl/min.

10. The method of claim 7, wherein the flow rate of said agents is between about 1 μl/min and about 2 μl/min.

11. The method of claim 7, wherein the flow rate of said agents is about 1 μl/min.

12. The method of claim 7, wherein said agents flow through said microdialysis probe(s) in a continuous fashion.

13. The method of claim 7, wherein said flow is carried out with a peristaltic pump.

14. The method of claim 7, wherein said flow spans a pre-determined period of time.

15. The method of claim 14, wherein said pre-determined period of time is at least about one hour.

16. The method of claim 14, wherein said pre-determined period of time is from about one hour to about one year.

17. The method of any one of claims 1, 2, and 3, wherein at least one of said agent(s) is delivered to a same region of said solid tissue in multiple doses.

18. The method of claim 17, wherein any two of said multiple doses are separated by a selected period of time.

19. The method of claim 18, wherein said selected period of time is at least about 10 minutes.

20. The method of claim 18, wherein said selected period of time is from about one hour to about three months.

21. The method of any one of claims 1, 2 and 3, wherein said agent(s) comprises a chemotherapeutic agent.

22. The method of any one of claim 1, 2 and 3, wherein said agent(s) comprises a small molecule agent.

23. The method of claim 22, wherein said small molecule agent has a molecular weight of less than 10^3 daltons.

24. The method of any one of claims 1, 2 and 3, wherein said agent(s) comprises an agent that interferes with RNA activity.

25. The method of any one of claims 1, 2 and 3, wherein said agent(s) comprises a gene therapy agent.

26. The method of any one of claims 1, 2 and 3, wherein said agent(s) comprises an agent selected from the group consisting of a protein, a peptide, a peptidomimetic, an antibody, a small molecule, a small interfering RNA-encoding polynucleotide, an antisense RNA-encoding polynucleotide, or a ribozyme-encoding polynucleotide.

27. The method of any one of claims 1, 2 and 3, wherein said agent(s) comprises a fluorescent dye.

28. The method of any one of claims 1, 2 and 3, wherein two or more agents are delivered simultaneously to a same region within said solid tissue.

29. The method of any one of claims 1, 2 and 3, wherein two or more agents are delivered sequentially to a same region within said solid tissue.

30. The method of any one of claims 1, 2 and 3, wherein two or more agents are delivered to different regions within said solid tissue.

31. The method of any one of claims 1, 2 and 3, wherein at least one agent is delivered to different regions within said solid tissue at different concentrations.

32. The method of any one of claims 1, 2 and 3, wherein said solid tissue comprises a tumor.

33. The method of claim 32, wherein said tumor is selected from the group consisting of a benign tumor and a malignant tumor.

34. The method of claim 32, wherein said tumor is selected from the group consisting of a primary tumor, an invasive tumor and a metastatic tumor.

35. The method of claim 32, wherein said tumor comprises at least one cancer cell selected from the group consisting of a prostate cancer cell, a breast cancer cell, a colon cancer cell, a lung cancer cell, a brain cancer cell, and an ovarian cancer cell.

36. The method of claim 32, wherein said tumor comprises a cancer selected from the group consisting of adenoma, adenocarcinoma, squamous cell carcinoma, basal cell carcinoma, small cell carcinoma, large cell undifferentiated carcinoma, chondrosarcoma, and fibrosarcoma.

37. The method of any one of claims 1, 2 and 3, wherein said solid tissue is selected from the group consisting of brain, liver, lung, kidney, prostate, ovary, spleen, lymph node, thyroid, pancreas, heart, skeletal muscle, intestine, larynx, esophagus, and stomach.

38. The method of claim 4, wherein said evaluating is performed in vitro.

39. The method of claim 4, wherein said evaluating is performed in vivo.

40. The method of claim 4, wherein said evaluating comprises histology sectioning.

41. The method of claim 4, wherein said evaluating comprises detecting activity or toxicity or lack thereof of each of said agent(s), when not delivered systemically, in separate regions of said solid tissue.

42. The method of claim 4, wherein said evaluating comprises detecting the activity or toxicity of at least two of said agents, when not delivered systemically, in a same region of said solid tissue.

43. The method of claim 42, wherein said activity or toxicity is synergistic.

44. The method of claim 42, wherein said activity or toxicity is additive.

45. The method of claim 4, wherein said evaluating comprises imaging said solid tissue.

46. The method of claim 45, wherein said imaging comprises radiographic imaging, magnetic resonance imaging, positron emission tomography, or biophotonic imaging.

47. The method of claim 45, wherein said imaging occurs during, or after introduction of said agents.

48. The method of claim 4, wherein said evaluating comprises collecting and analyzing at least one analyte selected from the group consisting of a biomarker for tumor cell death, cell signal changes, or proliferation/mitotic changes, the agent(s) delivered to the solid tissue and metabolite(s) of the agent(s) delivered to the solid tissue.

49. The method of claim 4, wherein said evaluating comprises detecting an effect of said agent(s) on a proliferative gradient or multiple microenvironments of said solid tissue.

50. The method of any one of claims 1, 2 and 3, wherein at least a portion of said microdialysis probe(s) spanning said solid tissue comprises a semi-permeable membrane.

51. The method of any one of claims 1, 2 and 3, further comprising marking sites of insertions.

52. The method of claim 51, wherein said sites of insertions are marked by at least one position marker.

53. The method of claim 52, wherein said at least one position marker comprises a dye.

54. The method of claim 53, wherein said dye and at least one additional agent is delivered to a same region within said solid tissue.

55. The method of any one of claims 1, 2 and 3, wherein said inserting is directed by an array guide.

56. The method of any one of claims 1, 2 and 3, wherein said inserting is carried out with a needle array device.

57. The method of claim 56, wherein said needle array device comprises at least two needles.

58. The method of claim 56, wherein said needle array device comprises at least five needles.

59. The method of claim 56, wherein said needle array device comprises at least ten needles.

60. The method of claim 1 or 3, wherein said microdialysis probe(s) comprises at least three microdialysis probes.

61. The method of claim 1 or 3, wherein said microdialysis probe(s) comprises at least five microdialysis probes.

62. The method of claim 1 or 3, wherein said microdialysis probe(s) comprises at least ten microdialysis probes.

63. The method of any one of claims 1, 2 and 3, wherein each of said microdialysis probe(s) or each of said needle(s) when there are two or more needles or microdialysis probes present contains a different agent.

64. The method of any one of claims 1, 2 and 3, wherein at least two of said microdialysis probes or needles when there are two or more needles or microdialysis probes present each contains a same agent at different concentrations.

65. The method of any one of claims 1, 2 and 3, wherein said agent(s) is delivered along an axis to said solid tissue.

66. The method of claim 65, wherein said axis is one of a plurality of parallel axes within said solid tissue.

67. The method of claim 4, wherein at least one of said agent(s) is a cancer therapeutic agent.

68. The method of claim 67, wherein said evaluating comprises detecting cell apoptosis after delivering said cancer therapeutic agent.

69. The method of claim 68, wherein said cell apoptosis is detected in a region of within 5 mm from site of delivery.

70. The method of claim 69, wherein said cancer therapeutic agent is deselected from further evaluation if less than 20% cell apoptosis is observed comparing to a control without said agent.

71. The method of claim 69, wherein said cancer therapeutic agent is deselected from further evaluation if less than 80% cell apoptosis is observed comparing to a control without said agent.

72. The method of claim 69, wherein said cancer therapeutic agent is selected for further evaluation if more than 50% cell apoptosis is observed comparing to a control without said agent.

73. The method of claim 69, wherein said cancer therapeutic agent is selected for further evaluation if more than 80% cell apoptosis is observed comparing to a control without said agent.

74. The method of claim 2, wherein said withdrawing one or more needles and injecting one or more agents are carried out simultaneously.

75. The method of claim 2, wherein the rate of injecting one or more agents is at least about 0.1 μl/min.

76. The method of claim 2, wherein the rate of injecting one or more agents is between about 0.1 μl/min and about 10 μl/min.

77. The method of claim 2, wherein the rate of injecting one or more agents is about 0.5 μl/min.

78. The method of claim 2, wherein the rate of injecting one or more agents is about 1μl/min.

79. The method of claim 2, wherein the rate of withdrawing one or more needles is at least about 0.1 mm/min.

80. The method of claim 2, wherein the rate of withdrawing one or more needles is between about 0.1 mm/min and about 5 mm/min.

81. The method of claim 2, wherein the rate of withdrawing one or more needles is about 0.5 mm/min.

82. The method of claim 2, wherein said one or more needles comprise at least three needles.

83. The method of claim 2, wherein said one or more needles comprise at least five needles.

84. The method of claim 2, wherein said one or more needles comprise at least ten needles.

85. The method of claim 2, wherein said one or more needles comprises an end-port needle.

86. The method of claim 2, further comprising one or more reservoirs each in fluid communication with a respective one of said one or more needles.

87. The method of claim 2, further comprising two or more reservoirs each in fluid communication with one of said one or more needles.

88. The method of claim 2, further comprising five or more reservoirs each in fluid communication with one of said one or more needles.

89. The method of any one of claims 1, 2 and 3, wherein outside said solid tissue said agent(s) is either (i) undetectable, or (ii) if detectable outside said solid tissue, said agent is present at less than a minimal effective dose.

90. The method of any one of claims 1, 2 and 3, wherein said agent(s) is introduced in an amount that is less than a minimal dose required to produce a detectable effect in said solid tissue.

91. The method of any one of claims 1, 2 and 3, wherein said agent(s) is present in said solid tissue at a therapeutically effective concentration.

92. The method of claim 3, wherein said at least one agent administered in (a) is present below a therapeutically effective concentration in systemic circulation.

93. The method of claim 3, wherein at least one agent delivered in (b) is delivered at different concentration to different regions of said solid tissue.

94. The method of claim 3, wherein at least one agent delivered in (b) is delivered in multiple doses to a same region of said solid tissue.

95. The method of claim 3, wherein the agent(s) delivered in (a) is selected from the group consisting of an anti-angiogenic agent, a kinase inhibitor, an inhibitor of metabolic pathway targets that are preferentially expressed in cancer cells, an antibody or antibody drug conjugate, or an epigenetic modifier.

96. The method of claim 3, wherein the agent(s) delivered in (b) comprises a small interfering RNA polynucleotide or an antisense RNA polynucleotide.

97. The method of claim 92, wherein the agent(s) in step (a) and the agent(s) in step (b) have synergistic effects on said solid tissue.

98. The method of claim 4, wherein the subject is an animal.

99. The method of claim 4, wherein the subject is a human.

100. The method of claim 98 or 99, further comprising one of (i) selecting at least one of said agent(s) based on the evaluating, (ii) deselecting at least one of the agent(s) based on the evaluating, and (iii) prioritizing at least two of the agents based on the evaluating.

101. The method of claim 4, wherein said subject is one of a plurality of subjects.

102. The method of claim 101, further comprising one of (i) selecting at least one of said plurality of subjects based on the evaluating, (ii) deselecting at least one of said plurality of subjects based on the evaluating, and (iii) prioritizing at least two of said plurality of subjects based on the evaluating.

103. A device for delivering a plurality of agents to a solid tissue of a subject, comprising a plurality of microdialysis probes.

104. The device of claim 103, further comprising a plurality of needles, each configured to receive one of said plurality of microdialysis probes.

105. The device of claim 104, further comprising at least one controller, operatively coupled to said plurality of needles.

106. The device of claim 103, wherein said controller is a computer system.

107. The device of claim 103, comprising at least 3 microdialysis probes.

108. The device of claim 103, comprising at least 4 microdialysis probes.

109. The device of claim 103, comprising at least 5 microdialysis probes.

110. The device of claim 103, comprising at least 6 microdialysis probes.

111. The device of claim 103, comprising at least 10 microdialysis probes.

112. The device of claim 104, comprising at least 3 needles.

113. The device of claim 104, comprising at least 4 needles.

114. The device of claim 104, comprising at least 5 needles.

115. The device of claim 104, comprising at least 6 needles.

116. The device of claim 104, comprising at least 10 needles.

117. The device of claim 104, further comprising a guiding device to guide the insertion of said plurality of needles to said solid tissue.

118. A device, comprising a top block having a first plurality of holes sized to allow a needle to pass through said top block and a bottom block having a second plurality of holes sized to allow a needle to pass through said bottom block, wherein said top and bottom blocks are in a

substantially parallel arrangement and wherein said first and second plurality of holes are positioned so as to allow one or more needles to pass through a hole in said top block and said bottom block in a path substantially vertical to the plane of both blocks.

119. The device of claim 118, further comprising at least one adjustable leg, wherein the at least one adjustable leg is attached to the bottom block.

120. The device of claim 119, comprising four adjustable legs.

121. The device of claim 119, wherein said at least one adjustable leg is vertically and horizontally adjustable.

122. The device of claim 118, wherein said bottom block is stationary.

123. The device of claim 118, wherein said top block moves vertically relative to said bottom block.

124. The device of claim 118, wherein said top block moves along guide rods attached to said bottom block.

125. The device of claim 118, further comprising a drive mechanism to control vertical movement of said top block.

126. The device of claim 118, wherein said first and second plurality of holes are arranged in substantially parallel rows.

127. The device of claim 118, further comprising at least one needle, wherein at least one of said first plurality of holes and at least one of said second plurality of holes are configured to receive said at least one needle.

128. The device of claim 127, wherein a control attachment is attached to the at least one needle.

129. The device of claim 128, wherein said control attachment stops the insertion of said at least one needle, thereby controlling depth of needle insertion into said solid tissue.

130. The device of claim 129, further comprising at least one spring, wherein said at least one spring is in substantial contact with said at least one adjustable leg and said bottom block.

131. A method of delivering at least one agent into a solid tissue, comprising:

(a) providing a device of claim 118;

(b) inserting one or more needles into said solid tissue using said device; and

(c) injecting said one or more agents into said solid tissue and withdrawing said one or more

needles from said solid tissue using said device.

132. The method of claim 131, further comprising evaluating an effect of at least one of said one or more agents on said solid tissue.

133. The method of claim 131, wherein said one or more needles comprise at least two needles.

134. The method of claim 131, wherein said one or more needles comprise at least five needles.

135. The method of claim 131, wherein said one or more needles comprise at least ten needles.

CLAIMS

1. A device for delivering one or more agents into a solid tissue comprising: one or more needles arranged in an array, wherein said one or more needles comprise one or more agents, and wherein said one or more agents are delivered to said solid tissue by withdrawing said one or more needles from said solid tissue.

2. The device of claim 1, wherein at least one of said one or more agents is delivered to a same region of said solid tissue in multiple doses.

3. The device of claim 2, wherein any two of said multiple doses are separated by a selected period of time.

4. The device of claim 1, wherein said one or more agents comprises a chemotherapeutic agent.

5. The device of claim 1, wherein said one or more agents comprises an agent selected from the group consisting of a protein, a peptide, a peptidomimetic, an antibody, a small molecule, a small interfering RNA-encoding polynucleotide, an antisense RNA-encoding polynucleotide, or a ribozyme-encoding polynucleotide.

6. The device of claim 1, wherein said one or more agents comprises a fluorescent dye.

7. The device of claim 1, wherein two of said one or more agents are delivered simultaneously to a same region within said solid tissue.

8. The device of claim 1, wherein two of said one or more agents are delivered sequentially to a same region within said solid tissue.

9. The device of claim 1, wherein two of said one or more agents are delivered to different regions within said solid tissue.

10. The device of claim 1, wherein at least one of said one or more agents is delivered to different regions within said solid tissue at different concentrations.

11. The device of claim 1, wherein said solid tissue comprises a tumor.

12. The device of claim 11, wherein said tumor is selected from the group consisting of a primary tumor, an invasive tumor and a metastatic tumor.

13. The device of claim 1, wherein sites of insertion are marked by said one or more needles.

14. The device of claim 13, wherein said sites of insertions are marked by at least one position marker.

15. The device of claim 14, wherein said at least one position marker comprises a dye.

16. The device of claim 15, wherein said dye and at least one additional agent is delivered to a same region within said solid tissue.

17. The device of claim 1, wherein each of said one or more needles comprises a different agent.

18. The device of claim 1, wherein at least two of said needles each comprises a same agent at different concentrations.

19. The device of claim 1, wherein said withdrawing one or more needles and injecting one or more agents are carried out simultaneously.

20. The device of claim 1, wherein said one or more needles comprise at least five needles.

21. The device of claim 1, wherein outside said solid tissue said one or more agents is undetectable outside said solid tissue.

22. The device of claim 1, wherein outside said solid tissue said one or more agents is introduced in an amount that is less than a minimal dose required to produce a detectable effect in said solid tissue.

23. The device of claim 1, wherein said one or more agents is present in said solid tissue at a therapeutically effective concentration.

24. The device of claim 1, wherein outside said solid tissue said one or more agents is present at less than a minimal effective dose.