Extrusion Methods and Devices for Drug Delivery

TECHNICAL FIELD

[0001] *In general, the disclosed embodiments relate to methods and devices for the introduction and subsequent evaluation of agents to solid tissue, and in particular to the simultaneous introduction of a plurality of agents to the tissue in vivo.*

BACKGROUND

[0002] The cost of new drug development from discovery through phase III trials is estimated to be between $800 million and $1.7 billion and the process can take between eight and ten years. Despite success in classical anticancer models, many cancer therapeutics do not reach the clinic. Numerous drug candidates fail during clinical trials. 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%.

[0003] There is a need in the art for improved methods and devices for delivering and evaluating cancer therapeutics. The present invention addresses these and needs, and offer other related advantages.

SUMMARY OF THE INVENTION

In one aspect, there is provided a device for delivering one or more agents to a solid tissue, comprising:

a. two or more needles, wherein said two or more needles comprise a first end and a second end;

b. a reservoir, wherein said reservoir is in fluid communication with said first end of said two or more needles;

c. a plunger, wherein said plunger is coupled to said reservoir; and

d. a controller, wherein said controller controls a rate of fluid delivery, wherein withdrawal of at least one of said two or more needles from said solid tissue occurs simultaneously with delivery of at least one of said one or more agents to said solid tissue.

In one aspect, the disclosure provides for a device, comprising a top block having a first plurality of holes sized to allow a needle to pass through the top block and a bottom block having a second plurality of holes sized to allow a needle to pass through the bottom

block, wherein the top and bottom blocks are in a substantially parallel arrangement and wherein the first and second plurality of holes are positioned so as to allow one or more needles to pass through a hole in the top block and the bottom block in a path substantially vertical to the plane of both blocks. In some embodiments, the device further comprises at least one adjustable leg, wherein the at least one adjustable leg is attached to the bottom block. In some embodiments, there are four adjustable legs. In some embodiments, the at least one leg is vertically and horizontally adjustable. In some embodiments, the bottom block is stationary. In some embodiments, the top block moves vertically relative to the bottom block. In some embodiments, the top block moves along guide rods attached to the bottom block. In some embodiments, the device further comprises a system to control vertical movement of the top block. In some embodiments, the first and second plurality of

CLAIMS

WHAT IS CLAIMED IS:

1. A device, comprising a top block having a first plurality of holes sized to allow a needle to pass through the top block and a bottom block having a second plurality of holes sized to allow a needle to pass through the bottom block, wherein the top and bottom blocks are in a substantially parallel arrangement and wherein the first and second plurality of holes are positioned so as to allow one or more needles to pass through a hole in the top block and the bottom block in a path substantially vertical to the plane of both blocks.
2. The device of claim 1, further comprising at least one adjustable leg, wherein the at least one adjustable leg is attached to the bottom block.
3. The device of claim 2, wherein there are four adjustable legs.
4. The device of claim 2, wherein the at least one leg is vertically and horizontally adjustable.
5. The device of claim 1, wherein the bottom block is stationary.
6. The device of claim 1, wherein the top block moves vertically relative to the bottom block.
7. The device of claim 6, wherein the top block moves along guide rods attached to the bottom block.
8. The device of claim 6, further comprising a system to control vertical movement of the top block.
9. The device of claim 1, wherein the first and second plurality of holes are arranged in substantially parallel rows.
10. The device of claim 1, further comprising at least one needle.
11. The device of claim 10, wherein a control attachment is attached to the at least one needle.
12. The device of claim 11, wherein the control attachment stops the insertion of the at least one needle, thereby controlling depth of needle insertion into the solid tissue.
13. The device of claim 2, further comprising at least one spring, wherein the at least one spring is in substantial contact with the adjustable leg and the bottom block.
14. The device of claim 1, further comprising a guiding rod that penetrates the bottom block.

15. The device of claim 14, wherein the guiding rod is inserted into a solid tissue.
16. The device of claim 14, wherein the guiding rod positions the needles on a solid tissue.

17. A device, comprising a top block having a first plurality of holes sized to allow a needle to pass through the top block and a bottom block having a second plurality of holes sized to allow a needle to pass through the bottom block, wherein the top and bottom blocks are in a substantially parallel arrangement and wherein the first and second plurality of holes are positioned so as to allow one or more needles to pass through a hole in the top block and the bottom block in a path substantially vertical to the plane of both blocks.
18. A method of operating a device of claim 1, comprising:
    a. inserting one or more needles through the top block and the bottom block into a solid tissue, wherein at least one needle has a control attachment;
    b. simultaneously move the top block away from the bottom block and injecting at least one agent into the solid tissue.
19. The method of claim 18, wherein the at least one needle is inserted into the solid tissue *in vivo*.
20. The method of claim 18, wherein the solid tissue is a tumor.
21. The method of claim 18, wherein the control attachment controls the depth of needle insertion.
22. The method of claim 18, wherein the at least one agent is injected in a column.
23. The method of claim 22, wherein the length of the column is from 1-10 millimeters.
24. The method of claim 18, wherein the one or more needles comprises at least two needles.
25. The method of claim 18, wherein the one or more needles comprises at least five needles.
26. A method of evaluating at least one agent in a solid tissue, comprising:
    a. placing at least a portion of the solid tissue under the device of claim 1;
    b. inserting one or more needles through the top block and the bottom block into the solid tissue, wherein at least one needle has a control attachment;
    c. simultaneously move the top block away from the bottom block;
    d. injecting at least one agent into the solid tissue; and

e. evaluating an effect of the at least one agent.

27. The method of claim 26, wherein the solid tissue is from a human, a mouse or a rat.
28. The method of claim 26, wherein the plurality of agents comprises an agent selected from a protein agent, a peptide agent, a polypeptide agent, a peptidomimetic agent, an antibody agent, a small molecule agent, a small interfering RNA-encoding polynucleotide, an antisense RNA-encoding polynucleotide, or a ribozyme-encoding polynucleotide.
29. The method of claim 26, wherein the at least one agent comprises a plurality of agents.
30. The method of claim 26, wherein the method is performed in an organism.
31. The method of claim 30, wherein the at least one agent has been systemically delivered to the organism.
32. The method of claim 29, wherein the plurality of agents comprises a chemotherapeutic agent.
33. The method of claim 29, wherein the plurality of agents comprises a small molecule agent.
34. The method of claim 29, wherein the plurality of agents comprises an agent that interferes with RNA activity.
35. The method of claim 29, wherein the plurality of agents comprises an anticancer agent.
36. The method of claim 29, wherein the plurality of agents further comprise at least one position marker.
37. The method of claim 36, wherein the at least one position marker is selected from the group consisting of a fluorescent dye, a nanoparticle, a GCMS tag molecule, a positive control, and a negative control.
38. The method of claim 36, wherein the at least one position comprise a fluorescent dye.
39. The method of claim 26, wherein at least two agents are injected into a same location.
40. The method of claim 26, wherein the rate of injecting at least one agent is at least 0.1 μl/min.
41. The method of claim 26, wherein the rate of injecting at least one agent is in the range of about 0.4 to about 4 μl/min.

42. The method of claim 26, wherein the rate of the movement of the top block is at least 0.1 mm/min.
43. The method of claim 26, wherein the rate of the movement of the top block is in the range of about 0.5 to about 5 mm/min.
44. The method of claim 26, wherein the solid tissue is a tumor.
45. The method of claim 44, wherein the 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.
46. The method of claim 44, wherein the 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.
47. The method of claim 29, wherein the plurality of agents is delivered to spatially defined locations within the solid tissue.
48. The method of claim 29, wherein the plurality of agents is delivered along parallel axes within the solid tissue.
49. The method of claim 29, wherein the plurality of agent is delivered to column-shaped regions along parallel axes within the solid tissue.
50. The method of claim 26, wherein the one or more needles comprises at least 2 needles.
51. The method of claim 26, wherein the one or more needles comprises at least 5 needles.
52. The method of claim 26, wherein the one or more needles comprises at least 10 needles.
53. The method of claim 26, wherein the evaluation comprises detecting an altered physiological state of the solid tissue.
54. The method of claim 26, wherein the evaluation comprises detecting the activity or toxicity of the at least one agents on the solid tissue.
55. The method of claim 26, wherein the evaluation comprises imaging the solid tissue.
56. The method of claim 55, wherein the imaging comprises radiographic imaging, magnetic resonance imaging, positron emission tomography, or biophotonic imaging.

57. The method of claim 55, wherein the imaging occurs before, during, or after introduction of the plurality of the at least one agent.
58. The method of claim 26, wherein the evaluation comprises histology sectioning.
59. The method of claim 26, wherein the evaluation comprises determining an effect of at least two agents on a same position within the region of the solid tissue.
60. The method of claim 26, wherein the evaluation comprises determining an effect of at least two agents on adjacent position within the region of the solid tissue.
61. The method of claims 50-52, wherein the needles are part of a needle array device.

62. A device for delivering an agent to a solid tissue, comprising:
    a. a plurality of needles, wherein one or more needles of said plurality of needles have a first end and a second end;
    b. a reservoir, wherein said reservoir is in fluid communication with said first end of said one or more needles;
    c. a plunger, wherein said plunger is coupled to said reservoir; and
    d. a controller, wherein said controller controls the rate of fluid delivery when said one or more needles are withdrawn from said solid tissue.
63. The device of claim 62, further comprising a central placement needle.
64. The device of claim 63, wherein the placement needle determines the correct orientation of the device on the tumor.
65. The device of claim 63, wherein the placement needle is in fluid communication with the reservoir.
66. The device of claim 62, wherein said controller is coupled to said plunger.
67. The device of claim 62, wherein said agent is delivered to said solid tissue with said plunger being locked.
68. The device of claim 62, further comprising a loading mechanism, wherein said loading mechanism is fluidly coupled to the second end of said one or more needles.
69. The device of claim 68, wherein said loading mechanism comprises a Closed System Transfer Device (CSTD).
70. The device of claim 62, wherein said device is handheld.
71. The device of claim 62, further comprising a depth-control mechanism.
72. The device of claim 71, wherein said depth-control mechanism controls the depth of needle insertion.

73. The device of claim 62, wherein the one or more needles comprises 2 or more needles.
74. The device of claim 62, wherein the one or more needles comprises 5 or more needles.
75. The device of claim 62, wherein the one or more needles comprises 10 or more needles.
76. The device of any one of claims 73 to 75, wherein said needles are arranged along parallel axes.
77. The device of claim 62, wherein said one or more needles is an end-port needle.
78. The device of claim 62, wherein the reservoir comprises 2 or more reservoirs.
79. The device of claim 62, wherein the reservoir comprises 5 or more reservoirs.
80. The device of claim 62, wherein the reservoir comprises 10 or more reservoirs.
81. The device of claim 62, wherein the one or more needles comprises 2 or more needles and the reservoir comprises 2 or more reservoirs, and wherein each of said 2 or more reservoirs is in fluid communication with a different one of said 2 or more needles.
82. The device of claim 81, wherein each of said 2 or more reservoirs comprises a different agent.
83. The device of claim 62, further comprising a deairification mechanism.
84. The device of claim 83, wherein said deairification mechanism removes at least a portion of air bubbles from said reservoir during loading of said agent.
85. The device of claim 83, wherein said deairification comprises at least one compartment connected to said reservoir.
86. The device of claim 85, wherein said at least one compartment provides venting and pressure equalization during loading of said agent.
87. The device of claim 86, wherein said at least one compartment is sealed during agent delivery.
88. The device of claim 62, further comprising a guiding rod that penetrates the bottom block.
89. The device of claim 88, wherein the guiding rod is inserted into the solid tissue.
90. The device of claim 88, wherein the guiding rod positions the needles on the solid tissue.
91. A method of delivering an agent to a solid tissue of a subject, comprising:
    a. inserting a plurality of needles into said solid tissue; and

b. delivering said agent to said solid tissue, wherein rate of agent delivery is substantially controlled by the rate of needle withdrawal from said solid tissue.

92. The method of claim 91, wherein said delivering is carried out with a device according to any one of claims 62, 67 and 83.

93. The method of claim 91, wherein said agent is delivered during needle withdrawal from said solid tissue.

94. The method of claim 91, wherein said agent is delivered only during needle withdrawal from said solid tissue.

95. The method of claim 91, wherein said needle is part of a needle array device.

96. The method of claim 95, wherein said needle array device comprises 2 or more needles.

97. The method of claim 95, wherein said needle array device comprises 5 or more needles.

98. The method of claim 95, wherein said needle array device comprises 10 or more needles.

99. The method of claim 91, wherein said agent is delivered along an axis within said solid tissue.

100. The method of claim 99, wherein said axis is one of a plurality of parallel axes.

101. The method of claim 91, wherein said agent comprises an anti-cancer agent.

102. The method of claim 101, wherein said anti-cancer agent is a small molecular agent.

103. The method of claim 91, wherein said agent comprises a position marker.

104. The method of claim 91, wherein said agent comprises a negative control.

105. The method of claim 91, wherein said agent comprises a positive control.

106. The method of any one of claims 96-98, wherein each of said needles comprises a different agent.

107. The method of any one of claims 96-98, wherein at least two of said needles comprise a same agent at different concentration.

108. The method of claim 91, wherein the delivering comprises deliverying two agents to said solid tissue.

109. The method of claim 108, wherein said two agents are delivered to a same region within said solid tissue.

110. The method of claim 108, wherein said two agents are delivered to different regions within said solid tissue.

111. The method of claim 91, wherein said agent is present in said solid tissue at a therapeutically effective concentration.

112. The method of claim 111, wherein outside said solid tissue said agent is present at a concentration that is less than about 75% of the therapeutically effective concentration.

113. The method of claim 111, wherein at least one agent is present in said solid tissue at a therapeutically effective concentration, and outside said solid tissue said agent is present at a concentration that is less than about 90% of the therapeutically effective concentration.

114. The method of claim 111, wherein said agent is undetectable outside said solid tissue.

115. The method of claim 91, wherein said solid tissue comprises a tumor.

116. The method of claim 115, wherein said tumor is selected from the group consisting of a benign tumor and a malignant tumor.

117. The method of claim 115, wherein said tumor is selected from the group consisting of a primary tumor, an invasive tumor and a metastatic tumor.

118. The method of claim 115, wherein said tumor comprises at least one cancer cell selected from the group consisting of a prostate cancer cell, a lymph node cell, a breast cancer cell, a colon cancer cell, a lung cancer cell, a brain cancer cell, a melanoma cell, a sarcoma cell, and an ovarian cancer cell, or any combination thereof.

119. The method of claim 115, wherein said tumor comprises at least one cancer cell selected from the group consisting of a lymphoma cell, a breast cancer cell, a melanoma cell, and a sarcoma cell, or any combination thereof.

120. The method of claim 115, 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, lymphoma, sarcoma, and fibrosarcoma.

121. The method of claim 115, 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, skin and stomach.

122. The method of claim 91, further comprising evaluating an effect of said agent on said solid tissue.

123. The method of claim 122, wherein said evaluating is performed in vitro.

124. The method of claim 122, wherein said evaluating is performed in vivo.

125. The method of claim 122, wherein said evaluating comprises histology sectioning.

126. The method of claim 122, wherein said evaluating comprises imaging said solid tissue.

127. The method of claim 126, wherein said imaging comprises radiographic imaging, magnetic resonance imaging, positron emission tomogoraphy, or biophotonic imaging.

128. The method of claim 126, wherein said imaging occurs during, or after introduction of said agents.

129. The method of claim 122, wherein said evaluating comprises collecting and analyzing at least one biomarker for tumor cell death, cell signal changes, or proliferation/mitotic changes.

130. The method of claim 122, wherein said evaluating comprises detecting an effect of said one or more agents on a proliferative gradient or multiple microenvironments of said solid tissue.

131. The method of claim 122, wherein said evaluating comprises detecting at least one biomarker using Mass Spectrometry.

132. The method of claim 131, wherein said mass spectrometry is Imaging Mass Spectrometry.

133. The method of claim 103, wherein said position marker comprises infrared dyes.

134. The method of claim 103, wherein said position marker comprises fluorescent inks

135. The method of claim 103, wherein said positional marker comprises new methylene blue, isosulfan blue or rhodamina WT.

CLAIMS

WHAT IS CLAIMED IS:

1. A device for delivering one or more agents to a solid tissue, comprising:

a. two or more needles, wherein said two or more needles comprise a first end and a second end;

b. a reservoir, wherein said reservoir is in fluid communication with said first end of said two or more needles;

c. a plunger, wherein said plunger is coupled to said reservoir; and

d. a controller, wherein said controller controls a rate of fluid delivery, wherein withdrawal of at least one of said two or more needles from said solid tissue occurs simultaneously with delivery of at least one of said one or more agents to said solid tissue.

2. The device of claim 1, wherein said two or more needles are positioned in an array.

3. The device of claim 2, wherein said array comprises 5 or more needles.

4. The device of claim 3, wherein each of said 5 or more needles comprises a different agent.

5. The device of claim 2, wherein at least two of said two or more needles comprises a same agent at different concentrations.

6. The device of claim 1, wherein at least one of said one or more agents comprises an anti-cancer agent.

7. The device of claim 6, wherein said anti-cancer agent comprises a small molecular agent.

8. The device of claim 1, wherein at least one of said one or more agents comprises a position marker.

9. The device of claim 1, wherein at least one of said one or more agents comprises a negative control.

10. The device of claim 1, wherein at least one of said one or more agents comprises a positive control.

11. The device of claim 1, wherein at least one of said one or more agents is delivered to said solid tissue at a therapeutically effective concentration.

12. The device of claim 1, wherein at least one of said one or more agents is delivered to said solid tissue in an amount that is undetectable outside said solid tissue.

13. The device of claim 1, wherein at least one of said one or more agents is delivered to said solid tissue at a therapeutically effective concentration, and wherein outside said solid tissue said at least one of said one or more agents is present at a concentration that is undetectable.

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

15. The device of claim 1, wherein at least one of said one or more agents comprises a chemotherapeutic.

16. The device of claim 1, wherein at least one of said one or more agents comprises tattoo ink.

17. The device of claim 1, wherein at least one of said two or more needles delivers said one or more agents by passive delivery.

18. The device of claim 1, wherein a rate of said withdrawal of said at least one of said two or more needles is controlled by said controller.

19. The device of claim 1, wherein a portion of said one or more agents is delivered when a needle is not being withdrawn from said solid tissue.

20. The device of claim 1, wherein said one or more agents are delivered to said solid tissue only during said withdrawal of said at least one of said two or more needles from said solid tissue.

21. The device of claim 1, wherein said one or more agents are delivered in a column.

22. The device of claim 21, wherein a length of said column is between about 1 to about 10 millimeters.

23. The device of claim 1, wherein said rate of delivery of said one or more agents is at least 0.1 microliter/minute.

24. The device of claim 1, wherein said rate of delivery of said one or more agents is in the range of about 0.4 to about 4 microliters/minute.

25. The device of claim 18, wherein said rate of needle withdrawal is at least 0.1 mm/min.

26. The device of claim 18, wherein said rate of needle withdrawal is in the range of about 0.5 to about 5 mm/min.