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).

Clearly there is a need in the art for improved devices and methods for testing and delivering cancer therapies, including improved methodologies for performing efficient pre-clinical and clinical studies of candidate oncology medicines, and for identifying therapeutics having increased likelihood of benefitting individual subjects. The present invention addresses these and similar needs, and offers other related advantages.

BRIEF SUMMARY

In one aspect, the present invention refers to a device for delivery of one or more agents into a solid tissue, comprising: a plurality of needles arranged in an array configured to deliver the one or more agents into the solid tissue along an axis of the plurality of needles; wherein the device is configured to deliver the one or more agents at less than a minimal dose required to produce a detectable effect in an adult, undetectable outside the solid tissue, or a therapeutically effective amount.

In another aspect, the present invention refers to a device for delivery of one or more agents into a solid tissue, comprising: a plurality of needles arranged in an array configured to deliver the one or more agents into the solid tissue along an axis of the plurality of needles; wherein the device is configured for passive delivery of the one or more agents into the solid tissue.

In yet another aspect, the present invention refers to a device for delivery of one or more agents into a solid tissue, comprising: a plurality of needles arranged in an array configured to deliver the one or more agents into the solid tissue along an axis of the plurality of needles; wherein an amount of agent in each of the plurality of needles is less than 1 μL per needle.

In a further aspect, the present invention refers to a device for delivery of one or more agents into a solid tissue, comprising: a plurality of needles arranged in an array configured to deliver the one or more agents into the solid tissue along an axis of the plurality of needles; wherein the device comprises more than one thousand needles.

In another aspect, the present invention refers to a device for delivery of one or more agents into a solid tissue, comprising: a plurality of needles arranged in an array *configured to deliver the one or more agents into the solid tissue along an axis of the* plurality of needles; wherein the device comprises needles coated with nanowire.

In yet another aspect, the present invention refers to a device for delivery of one or more agents into a solid tissue, comprising: a plurality of needles arranged in an array configured to deliver the one or more agents into the solid tissue along an axis of the plurality of needles; wherein the device comprises needles made from porous material.

It is an exampleaspect of the present disclosureinvention to describeprovide a device for delivery of a fluid to a solid tissue, comprising: a plurality of needles arranged in an array; a plurality of reservoirs, each in fluid communication with a respective one of the plurality of needles; and a plurality of actuators operatively coupled to respective ones of the plurality of reservoirs and configured to control a fluid pressure within the reservoir. In certain exampleembodiments each of the plurality of actuators comprises one of a plurality of plungers, a first end of each of the plurality of plungers being received in a respective one of the plurality of reservoirs, and in certain further exampleembodiments the plungers of the plurality of plungers are operatively coupled together at respective second ends so as to be simultaneously depressable. Certain still further exampleembodiments comprise a plunger driver configured to depress all of the plurality of plungers at a selectively variable rate. In other exampleembodiments each of the plurality of actuators comprises one of a plurality of fluid transmission lines having first and second ends, a first end of each of the plurality of fluid transmission lines being coupled to a respective one of the plurality of reservoirs. In other exampleembodiments the device comprises a fluid pressure source, and each of the plurality of

actuators comprises a fluid coupling between the fluid pressure source and a respective one of the plurality of reservoirs. In further exampleembodiments the fluid pressure source comprises at least one of a compressor, a vacuum accumulator, a peristaltic pump, a master cylinder, a microfluidic pump, and a valve. In another exampleembodiment, each of the plurality of needles comprises a plurality of ports distributed along its length.

In another exampleembodiment there is discloseprovided a device for delivering a fluid to a solid tissue, comprising a dispenser including a needle having a plurality of ports distributed along a length thereof, a reservoir in fluid communication with the dispensing needle, and a plunger having a first end positioned in the reservoir; and a plunger driver coupled to a second end of the plunger and configured to depress the plunger at a selectably variable rate. In certain further exampleembodiments the dispenser is one of a plurality of dispensers arranged in a dispenser array, each comprising a needle, a reservoir, and a plunger having first and second ends. In certain further exampleembodiments the plunger driver is coupled to the second end of the plunger of each of the plurality of dispensers and is configured to depress each of the plungers simultaneously. In certain other further exampleembodiments the device comprises a plurality of cylindrical tubes arranged in an array corresponding to the dispenser array, each of the plurality of cylindrical tubes being sized and positioned to receive the needle of a respective one of the plurality of dispensers.

In certain other exampleembodiments the plunger driver comprises a driver shaft coupled to the plunger and having a threaded region, the plunger driver configured such that rotation of the driver shaft in a first direction depresses the plunger a distance corresponding to a thread pitch of the threaded region and a number of revolutions of the driver shaft. In certain further exampleembodiments the device comprises a motor having a rotor coupled to the driver shaft of the plunger driver such that the rotor and the driver shaft are rotationally fixed with respect to each other, the motor being controllable to rotate the rotor at a selectably variable rate. In certain other further

exampleembodiments the device comprises a motor having a rotor coupled to the driver shaft of the plunger driver such that the rotor and the driver shaft are rotationally fixed with respect to each other, the motor being controllable to rotate the rotor to a selectable angle of rotation. Certain further exampleembodiments comprise a controller coupled to the motor, the controller being programmable to control direction and speed of rotation of the rotor and to control a number of degrees from a start of rotation to an end of rotation. In other exampleembodiments of the above described device, the dispenser comprises a dispenser cylinder; a first portion of the dispenser cylinder defines the reservoir; and a second portion of the dispenser cylinder defines the needle. In another exampleembodiment the plurality of ports are sized and positioned along the length of the needle so as to deliver a substantially equal amount of fluid at any given location along the length of the needle. In another exampleembodiment the plurality of ports is evenly distributed along a portion of the length of the needle.

In certain exampleembodiments a size of each of the plurality of ports is inversely related to a distance of the respective port from a tip-end of the needle. In certain other exampleembodiments a distribution density of the plurality of ports is inversely related to a distance of the respective port from a tip-end of the needle. In certain other exampleembodiments the plurality of ports is distributed in a spiral pattern along the length of the needle. In certain other exampleembodiments the plurality of ports is arranged in pairs of ports on opposite sides of the needle, with each pair of ports rotated 90 degrees with respect to adjacent pairs of ports along the length of the needle.

According to certain other exampleembodiments disclosed herein, there is discloseprovided a method, comprising placing an agent in a reservoir of each of a plurality of dispenser needles; inserting each of the plurality of dispenser needles into a selected region of solid tissue; and introducing the agent in the reservoirs into the selected region of solid tissue by simultaneously overpressurizing each of the plurality of dispenser needles. In certain further exampleembodiments the introducing comprises introducing the agent in the reservoirs

into the selected region of solid tissue from a plurality of apertures along each of the plurality of dispenser needles. Certain other further exampleembodiments comprise at least one of imaging the solid tissue prior to the inserting, imaging the solid tissue concurrently with the inserting, and imaging the solid tissue after the inserting. In certain other further exampleembodiments the inserting comprises inserting an array of introducer needles into a subject; inserting each of the plurality of dispenser needles into a respective one of the array of introducer needles; and extending a tip-end of each of the plurality of dispenser needles beyond a tip end of the respective one of the array of introducer needles and into the selected region of tissue. Certain further exampleembodiments comprise removing stylets from the introducer needles of the array prior to inserting the plurality of dispenser needles.

In certain exampleembodiments the selected region of tissue is a portion of a tumor in a subject, and in certain further exampleembodiments the subject is one of a preclinical model and a human patient. In certain other exampleembodiments the method comprises excising at least the portion of the tumor after the introducing. Certain further exampleembodiments comprise at least one of imaging the tumor prior to the excising, imaging the tumor concurrently with the excising, and imaging the tumor after to the excising. In certain other exampleembodiments the excising comprises excising at least the portion of the tumor at a time that is a selected period of time after introducing the agent. In certain further exampleembodiments the selected period of time is one of a range of time, a minimum period of time for excising, and a specific period of time for excising. In certain exampleembodiments the selected period of time is a period exceeding 48 hours. In certain exampleembodiments the selected period of time is a range of between about 72 and about 96 hours. In certain exampleembodiments the selected period of time is a period exceed one week.

According to certain other exampleembodiments of the above described method, the agent comprises a plurality of agents, and the placing comprises placing each of the plurality of agents into the reservoir of a respective one of

the plurality of dispenser needles. In certain further exampleembodiments the plurality of agents comprises at least one of a negative control composition and a positive control composition. In certain other further exampleembodiments the plurality of agents comprises at least one position marker. In certain other further exampleembodiments at least one of the plurality of agents is a candidate effective agent. In certain other further exampleembodiments at least one of the plurality of agents comprises an indicator of efficacy, which in certain further exampleembodiments comprises at least one of a nanoparticle, a nanostucture, and an indicator dye. In certain other exampleembodiments at least one of the plurality of agents is selected based on a clinically demonstrated efficacy of the respective agent. In certain other further exampleembodiments of the above described method, the method comprises assessing, with respect to at least one of the plurality of agents, at least one of efficacy, activity, and toxicity of the agent.

In another exampleembodiment there is discloseprovided a method for identifying relative efficacies of a plurality of agents for treating a subject, comprising injecting each of a plurality of candidate effective agents into a respective location in an injection site in a solid tissue in a subject; excising from the subject at least the injection site of the solid tissue; and evaluating the excised injection site for an altered physiologic state at each of the respective locations, and therefrom identifying relative efficacies of the plurality of agents. In certain further exampleembodiments the excising comprises one of excising at least 48 hours after the injecting, excising at least 72 hours after the injecting, excising 72 to 96 hours after the injecting, and excising at least one week after the injecting.

In another exampleembodiment there is discloseprovided a method of operation of a therapeutic device, comprising charging a reservoir of each of a plurality of needles with a respective one of a plurality of agents; injecting, simultaneously, each of the plurality of agents into a respective region of a solid tissue; and evaluating an effect of each of the plurality of agents on the respective region. In certain further exampleembodiments the injecting comprises injecting the plurality of agents into the solid tissue *in vivo*, and in certain still further exampleembodiments the

method comprises excising the solid tissue prior to the evaluating. In certain exampleembodiments the method comprises imaging the solid tissue, which in certain further exampleembodiments comprises imaging the solid tissue *in vivo*. In certain other exampleembodiments the injecting comprises distributing each of the plurality of agents into the solid tissue along an axis in the respective region of the tissue. In certain other exampleembodiments the method further comprises assessing, with respect to at least one of the plurality of agents, at least one of efficacy, activity, and toxicity of the agent.

Also disclose~~provided~~ herein according to certain exampleembodiments is a method of determining efficacy of a cancer treatment regimen, comprising simultaneously introducing an agent to a plurality of positions in a solid tumor in a subject *in vivo*; removing the tumor from the subject; and evaluating an effect of the agent on the tumor *in vitro*. In certain further exampleembodiments the agent comprises a plurality of agents and the introducing comprises distributing each of the plurality of agents to a respective one of the plurality of positions in the tumor. In another exampleembodiment there is disclose~~provided~~ a method, comprising introducing an agent to a region of solid tissue in a subject by distributing the agent to a plurality of positions along an axis within the region of solid tissue *in vivo*; removing the region of solid tissue from the subject; and evaluating an effect of the agent on the region of solid tissue *in vitro*. In a further exampleembodiment the region of solid tissue comprises a tumor.

In certain exampleembodiments the axis is one of a plurality of parallel axes in the region of solid tissue, and wherein the introducing comprises distributing the agent along each of the plurality of parallel axes. In certain further exampleembodiments the introducing comprises simultaneously distributing the agent along each of the plurality of parallel axes, and in certain other further exampleembodiments the plurality of parallel axes is arranged in an array. In certain other exampleembodiments the method comprises introducing at least two position markers to the region of solid tissue along a respective one of the plurality of parallel axes, and in certain further exampleembodiments the introducing at least two

position markers comprises distributing the at least two position markers along respective parallel axes within the region of solid tissue. In certain other exampleembodiments the at least two position markers each comprise a detectable label that is selected from the group consisting of a radiolabel, a radio-opaque label, a fluorescent label, a colorimetric label, a dye, an enzymatic label, a GCMS tag, avidin, and biotin.

In certain other exampleembodiments of the above described method, the agent is one of a plurality of agents and the axis is one of a plurality of parallel axes arranged in an array in the region of solid tissue, and wherein the introducing comprises distributing each of the plurality of agents to a plurality of positions along a respective one of the plurality of parallel axes. In certain other exampleembodiment the method comprises at least one of imaging the solid tissue prior to the introducing, imaging the solid tissue concurrently with the introducing, and imaging the solid tissue after the introducing. In certain other exampleembodiments the evaluating comprises sectioning the region of solid tissue into a plurality of sections normal to the parallel axes. In certain further exampleembodiments the evaluating comprises detecting within the solid tissue an altered physiologic state that results from at least one of the plurality of agents. In certain further exampleembodiments the detecting comprises, with respect to the at least one of the plurality of agents, at least one of detecting a degree of permeation of the agent through the solid tissue, detecting a physicochemical effect of the agent on the tissue, and detecting a pharmacological effect of the agent on the tissue. In certain other exampleembodiments the evaluating comprises determining the effects of at least two of the plurality of agents on a same position within the region of the solid tissue. In certain other exampleembodiments the evaluating comprises determining the effects of at least two of the plurality of agents on adjacent positions within the region of the solid tissue.

In certain other exampleembodiments the evaluating comprises differentiating a degree of the effect of at least one of the plurality of agents on different sections of the solid tissue according to different characteristics of the

different sections of the solid tissue. In certain other exampleembodiments the evaluating comprises comparing a first effect of at least a first one of the plurality of agents on the solid tissue with a second effect of at least a second one of the plurality of agents on the solid tissue. In certain other exampleembodiments the evaluating comprises, with respect to at least one of the plurality of agents, assessing at least one of efficacy, activity, and toxicity on the region of solid tissue. In certain other exampleembodiments the method comprises deselecting at least one of the plurality of agents based on the evaluating. In certain other exampleembodiments the method comprises selecting at least one of the plurality of agents based on the evaluating. In certain other exampleembodiments the method comprises prioritizing at least two of the plurality of agents based on the evaluating. In certain other exampleembodiments the method comprises distributing the plurality of agents to a plurality of positions, each along a respective one of a plurality of parallel axes within a region of solid tissue within each of a plurality of subjects. In certain further exampleembodiments the method comprises one of (i) selecting at least one of the plurality of agents based on the evaluating, (ii) deselecting at least one of the plurality of agents based on the evaluating, and (iii) prioritizing at least two of the plurality of agents based on the evaluating. In certain other exampleembodiments the method comprises one of (i) selecting at least one of the plurality of subjects based on the evaluating, (ii) deselecting at least one of the plurality of subjects based on the evaluating, and (iii) prioritizing at least two of the plurality of subjects based on the evaluating. In certain other exampleembodiments the evaluating comprises determining a level of altered physiologic state of the solid tissue near at least one of the plurality of parallel axes.

Turning to another exampleembodiment there is discloseprovided a fluid agent-delivering device comprising (i) a plurality of needles arranged in an array, each of said needles having, independently, one or a plurality of ports distributed along its length wherein at least one needle has said plurality of ports, (ii) a plurality of reservoirs containing the fluid agent, each of said reservoirs being in

fluid communication with a respective one of the plurality of needles, and (iii) a plurality of plungers, a first end of each plunger being received in a respective one of the plurality of reservoirs and a second end of each plunger being depressable such that depressing each plunger results in injection of the fluid agent through the respective one of the plurality of needles.

In another exampleembodiment of the presently disclosureed invention there is describeprovided a method for selective delivery of a fluid agent to a solid tissue, comprising (a) introducing a plurality of needles of a fluid agent-delivering device into the solid tissue; and (b) administering the fluid agent into the solid tissue by injection through said needles. In certain further exampleembodiments the solid tissue has been removed from a subject. In certain other further exampleembodiments the solid tissue is in a subject. In certain further exampleembodiments the agent is delivered to the solid tissue in a therapeutically effective amount. In certain still further exampleembodiments, outside the solid tissue, the agent is either (i) undetectable, or (ii) if detectable outside the solid tissue, the agent is present at less than a minimal dose. In certain exampleembodiments the solid tissue comprises a tumor. In certain further exampleembodiments the tumor is selected from a benign tumor and a malignant tumor. In certain other further exampleembodiments the tumor is selected from a primary tumor, an invasive tumor and a metastatic tumor. In certain other further exampleembodiments the tumor comprises at least one cancer cell selected from 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. In certain other further exampleembodiments the tumor comprises a cancer selected from adenoma, adenocarcinoma, squamous cell carcinoma, basal cell carcinoma, small cell carcinoma, large cell undifferentiated carcinoma, chondrosarcoma and fibrosarcoma. In certain other exampleembodiments the solid tissue is selected from brain, liver, lung, kidney, prostate, ovary, spleen, lymph node, thyroid, pancreas, heart, skeletal muscle, intestine, larynx, esophagus and stomach.

In certain other exampleembodiments the fluid agent comprises an agent that is selected from (a) a gene therapy agent; (b) a chemotherapy agent; (c) a

small molecule; (d) an antibody; (e) a protein; (f) one of a small interfering RNA and an encoding polynucleotide therefor; (g) one of an antisense RNA and an encoding polynucleotide therefor; (h) one of a ribozyme and an encoding polynucleotide therefor; (i) a detectable label; and (j) one of a therapeutic protein, polypeptide, and a peptidomimetic. In certain further exampleembodiments the detectable label is selected from a radiolabel, a radio-opaque label, a fluorescent label, a colorimetric label, a dye, an enzymatic label, a GCMS tag, avidin, and biotin. In certain exampleembodiments the agent is selected from (i) a gene therapy agent that comprises at least one operably linked promoter, (ii) a small interfering RNA-encoding polynucleotide that comprises at least one operably linked promoter; (iii) an antisense RNA-encoding polynucleotide that comprises at least one operably linked promoter; and (iv) a ribozyme-encoding polynucleotide that comprises at least one operably linked promoter. In certain further exampleembodiments the operably linked promoter is selected from a constitutive promoter and a regulatable promoter. In certain still further exampleembodiments the regulatable promoter is selected from an inducible promoter, a tightly regulated promoter and a tissue-specific promoter.

In certain other exampleembodiments there is discloseprovided a method for altering a physiologic state in a solid tissue, comprising: (a) introducing a plurality of needles of a fluid agent-delivering device into the solid tissue; and (b) administering the fluid agent into the solid tissue by injection through said needles.

In certain exampleembodiments there is discloseprovided a method for obtaining biological samples from a plurality of positions in a solid tissue, comprising (a) introducing a multiple needle device into the solid tissue, thereby placing a plurality of needles at a plurality of positions in the tissue; and (b) generating negative pressure at a port of each needle of said multiple needle device under conditions and for a time sufficient to draw into said needles a plurality of biological samples from said plurality of positions in the tissue, and thereby obtaining biological samples from a plurality of positions in the tissue.

In certain exampleembodiments there is discloseprovided a method for obtaining biological samples from a plurality of positions along an axis in a solid tissue, comprising (a) introducing a multiple needle device into the solid tissue, thereby placing a plurality of needles at a plurality of positions in the tissue; and (b) generating negative pressure at a plurality of ports located along a length of each needle of said multiple needle device under conditions and for a time sufficient to draw into said needles a plurality of biological samples from said plurality of positions in the tissue, and thereby obtaining biological samples from a plurality of positions along an axis in the tissue.

In certain exampleembodiments there is discloseprovided a method of screening subjects for eligibility to participate in a clinical trial of one or more agents, comprising (a) introducing one or more agents to a region of solid tissue in one or more subjects *in vivo* by distributing each of said agents to a plurality of positions along an axis within the region in each subject; (b) removing the region of solid tissue from each of said subjects; and (c) evaluating each region removed in (b) for an effect of each agent on the respective position along the axis within the region, wherein either (i) for any given agent or agents presence of a detectable effect of said agent or agents on the solid tissue region from the subject indicates eligibility of the subject for participation in a clinical trial of the agent or agents, (ii) for any given agent or agents absence of a detectable effect of said agent or agents on the solid tissue region from the subject indicates ineligibility of the subject for participation in a clinical trial of the agent or agents, or (iii) both (i) and (ii).

In certain exampleembodiments there is discloseprovided a method of rating a candidate agent for development into a therapeutic agent for treating a solid tumor, comprising (a) introducing one or more candidate agents to a region of a solid tumor of known tumor type in each one or more subjects having a tumor of the known tumor type, by distributing each of said candidate agents to a plurality of positions along an axis within the region in each subject; (b) removing the region of solid tumor from each of said subjects; and (c)

CLAIMS

1. A device for delivery of a fluid to a solid tissue, comprising:

a plurality of needles arranged in an array;

a plurality of reservoirs, each in fluid communication with a respective one of the plurality of needles; and

a plurality of actuators operatively coupled to respective ones of the plurality of reservoirs and configured to control a fluid pressure within the reservoir.

2. The device of claim 1 wherein each of the plurality of actuators comprises one of a plurality of plungers, a first end of each of the plurality of plungers being received in a respective one of the plurality of reservoirs.

3. The device of claim 2 wherein the plungers of the plurality of plungers are operatively coupled together at respective second ends so as to be simultaneously depressable.

4. The device of claim 3, comprising a plunger driver configured to depress all of the plurality of plungers at a selectively variable rate.

5. The device of claim 1 wherein each of the plurality of actuators comprises one of a plurality of fluid transmission lines having first and second ends, a first end of each of the plurality of fluid transmission lines being coupled to a respective one of the plurality of reservoirs.

6. The device of claim 1, comprising a fluid pressure source, and wherein each of the plurality of actuators comprises a fluid coupling between the fluid pressure source and a respective one of the plurality of reservoirs.

7. The device of claim 6 wherein the fluid pressure source comprises at least one of a compressor, a vacuum accumulator, a peristaltic pump, a master cylinder, a microfluidic pump, and a valve.

8. The device of claim 1 wherein each of the plurality of needles comprises a plurality of ports distributed along its length.

9. A device for delivering a fluid to a solid tissue, comprising:

a dispenser including:

a needle having a plurality of ports distributed along a length thereof,

a reservoir in fluid communication with the dispensing needle, and

a plunger having a first end positioned in the reservoir; and

a plunger driver coupled to a second end of the plunger and configured to depress the plunger at a selectably variable rate.

10. The device of claim 9 wherein the dispenser is one of a plurality of dispensers arranged in a dispenser array, each comprising a needle, a reservoir, and a plunger having first and second ends.

11. The device of claim 10 wherein the plunger driver is coupled to the second end of the plunger of each of the plurality of dispensers and is configured to depress each of the plungers simultaneously.

12. The device of claim 10, comprising a plurality of cylindrical tubes arranged in an array corresponding to the dispenser array, each of the plurality of cylindrical tubes being sized and positioned to receive the needle of a respective one of the plurality of dispensers.

13. The device of claim 9 wherein the plunger driver comprises a driver shaft coupled to the plunger and having a threaded region, the plunger driver configured such that rotation of the driver shaft in a first direction depresses the plunger a distance corresponding to a thread pitch of the threaded region and a number of revolutions of the driver shaft.

14. The device of claim 13, comprising a motor having a rotor coupled to the driver shaft of the plunger driver such that the rotor and the driver shaft are rotationally fixed with respect to each other, the motor being controllable to rotate the rotor at a selectably variable rate.

15. The device of claim 13, comprising a motor having a rotor coupled to the driver shaft of the plunger driver such that the rotor and the driver shaft are rotationally fixed with respect to each other, the motor being controllable to rotate the rotor to a selectable angle of rotation.

16. The device of claim 15, comprising a controller coupled to the motor, the controller being programmable to control direction and speed of rotation of the rotor and to control a number of degrees from a start of rotation to an end of rotation.

17. The device of claim 9 wherein:

the dispenser comprises a dispenser cylinder;

a first portion of the dispenser cylinder defines the reservoir; and

a second portion of the dispenser cylinder defines the needle.

18. The device of claim 9 wherein the plurality of ports are sized and positioned along the length of the needle so as to deliver a substantially equal amount of fluid at any given location along the length of the needle.

19. The device of claim 9 wherein the plurality of ports is evenly distributed along a portion of the length of the needle.

20. The device of claim 9 wherein a size of each of the plurality of ports is inversely related to a distance of the respective port from a tip-end of the needle.

21. The device of claim 9 wherein a distribution density of the plurality of ports is inversely related to a distance of the respective port from a tip-end of the needle.

22. The device of claim 9 wherein the plurality of ports is distributed in a spiral pattern along the length of the needle.

23. The device of claim 9 wherein the plurality of ports is arranged in pairs of ports on opposite sides of the needle, with each pair of ports rotated 90 degrees with respect to adjacent pairs of ports along the length of the needle.

24. A method, comprising:

placing an agent in a reservoir of each of a plurality of dispenser needles;

inserting each of the plurality of dispenser needles into a selected region of solid tissue; and

introducing the agent in the reservoirs into the selected region of solid tissue by simultaneously overpressurizing each of the plurality of dispenser needles.

25. The method of claim 24 wherein the introducing comprises introducing the agent in the reservoirs into the selected region of solid tissue from a plurality of apertures along each of the plurality of dispenser needles.

26. The method of claim 24, comprising at least one of imaging the solid tissue prior to the inserting, imaging the solid tissue concurrently with the inserting, and imaging the solid tissue after the inserting.

27. The method of claim 24, wherein the inserting comprises:

inserting an array of introducer needles into a subject;

inserting each of the plurality of dispenser needles into a respective one of the array of introducer needles; and

extending a tip-end of each of the plurality of dispenser needles beyond a tip end of the respective one of the array of introducer needles and into the selected region of tissue.

28. The method of claim 27, comprising removing stylets from the introducer needles of the array prior to inserting the plurality of dispenser needles.

29. The method of claim 24 wherein the selected region of tissue is a portion of a tumor in a subject.

30. The method of claim 29 wherein the subject is one of a preclinical model and a human patient.

31. The method of claim 29, comprising excising at least the portion of the tumor after the introducing.

32. The method of claim 31 comprising at least one of imaging the tumor prior to the excising, imaging the tumor concurrently with the excising, and imaging the tumor after to the excising.

33. The method of claim 31 wherein the excising comprises excising at least the portion of the tumor at a time that is a selected period of time after introducing the agent.

34. The method of claim 33 wherein the selected period of time is one of a range of time, a minimum period of time for excising, and a specific period of time for excising.

35. The method of claim 33 wherein the selected period of time is a period exceeding 48 hours.

36. The method of claim 33 wherein the selected period of time is a range of between about 72 and about 96 hours.

37. The method of claim 33 wherein the selected period of time is a period exceeding one week.

38. The method of claim 24 wherein the agent comprises a plurality of agents, and the placing comprises placing each of the plurality of agents into the reservoir of a respective one of the plurality of dispenser needles.

39. The method of claim 38 wherein the plurality of agents comprises at least one of a negative control composition and a positive control composition.

40. The method of claim 38 wherein the plurality of agents comprises at least one position marker.

41. The method of claim 38 wherein at least one of the plurality of agents is a candidate effective agent.

42. The method of claim 38 wherein at least one of the plurality of agents comprises an indicator of efficacy.

43. The method of claim 42 wherein the indicator of efficacy comprises at least one of a nanoparticle, a nanostucture, and an indicator dye.

44. The method of claim 38, wherein at least one of the plurality of agents is selected based on a clinically demonstrated efficacy of the respective agent.

45. The method of claim 38, comprising assessing, with respect to at least one of the plurality of agents, at least one of efficacy, activity, and toxicity of the agent.

46. A method for identifying relative efficacies of a plurality of agents for treating a subject, comprising:

injecting each of a plurality of candidate effective agents into a respective location in an injection site in a solid tissue in a subject;

excising from the subject at least the injection site of the solid tissue; and

evaluating the excised injection site for an altered physiologic state at each of the respective locations, and therefrom identifying relative efficacies of the plurality of agents.

47. The method of claim 46 wherein the excising comprises one of excising at least 48 hours after the injecting, excising at least 72 hours after the injecting, excising 72 to 96 hours after the injecting, and excising at least one week after the injecting.

48. A method of operation of a therapeutic device, comprising:

charging a reservoir of each of a plurality of needles with a respective one of a plurality of agents;

injecting, simultaneously, each of the plurality of agents into a respective region of a solid tissue; and

evaluating an effect of each of the plurality of agents on the respective region.

49. The method of claim 48 wherein the injecting comprises injecting the plurality of agents into the solid tissue *in vivo*.

50. The method of claim 49, comprising excising the solid tissue prior to the evaluating.

51. The method of claim 49, comprising imaging the solid tissue.

52. The method of claim 51 wherein the imaging comprises imaging the solid tissue *in vivo*.

53. The method of claim 48 wherein the injecting comprises distributing each of the plurality of agents into the solid tissue along an axis in the respective region of the tissue.

54. The method of claim 48, comprising assessing, with respect to at least one of the plurality of agents, at least one of efficacy, activity, and toxicity of the agent.

55. A method of determining efficacy of a cancer treatment regimen, comprising:

simultaneously introducing an agent to a plurality of positions in a solid tumor in a subject *in vivo*;

removing the tumor from the subject; and

evaluating an effect of the agent on the tumor *in vitro*.

56. The method of claim 55 wherein the agent comprises a plurality of agents and the introducing comprises distributing each of the plurality of agents to a respective one of the plurality of positions in the tumor.

57. A method, comprising:

introducing an agent to a region of solid tissue in a subject by distributing the agent to a plurality of positions along an axis within the region of solid tissue *in vivo*;

removing the region of solid tissue from the subject; and

evaluating an effect of the agent on the region of solid tissue *in vitro*.

58. The method of claim 57 wherein the region of solid tissue comprises a tumor.

59. The method of claim 57 wherein the axis is one of a plurality of parallel axes in the region of solid tissue, and wherein the introducing comprises distributing the agent along each of the plurality of parallel axes.

60. The method of claim 59 wherein the introducing comprises simultaneously distributing the agent along each of the plurality of parallel axes.

61. The method of claim 59 wherein the plurality of parallel axes is arranged in an array.

62. The method of claim 57, comprising introducing at least two position markers to the region of solid tissue along a respective one of the plurality of parallel axes.

63. The method of claim 62 wherein the introducing at least two position markers comprises distributing the at least two position markers along respective parallel axes within the region of solid tissue.

64. The method of claim 62 wherein the at least two position markers each comprise a detectable label that is selected from the group consisting of a radiolabel, a radio-opaque label, a fluorescent label, a colorimetric label, a dye, an enzymatic label, a GCMS tag, avidin, and biotin.

65. The method of claim 57 wherein the agent is one of a plurality of agents and the axis is one of a plurality of parallel axes arranged in an array in the region of solid tissue, and wherein the introducing comprises distributing each of the plurality of agents to a plurality of positions along a respective one of the plurality of parallel axes.

66. The method of claim 57, comprising at least one of imaging the solid tissue prior to the introducing, imaging the solid tissue concurrently with the introducing, and imaging the solid tissue after the introducing.

67. The method of claim 65 wherein the evaluating comprises sectioning the region of solid tissue into a plurality of sections normal to the parallel axes.

68. The method of claim 67 wherein the evaluating comprises detecting within the solid tissue an altered physiologic state that results from at least one of the plurality of agents.

69. The method of claim 68 wherein the detecting comprises, with respect to the at least one of the plurality of agents, at least one of detecting a degree of permeation of the agent through the solid tissue, detecting a physicochemical effect of the agent on the tissue, and detecting a pharmacological effect of the agent on the tissue.

70. The method of claim 67 wherein the evaluating comprises determining the effects of at least two of the plurality of agents on a same position within the region of the solid tissue.

71. The method of claim 67 wherein the evaluating comprises determining the effects of at least two of the plurality of agents on adjacent positions within the region of the solid tissue.

72. The method of claim 67 wherein the evaluating comprises differentiating a degree of the effect of at least one of the plurality of agents on different sections of the solid tissue according to different characteristics of the different sections of the solid tissue.

73. The method of claim 67 wherein the evaluating comprises comparing a first effect of at least a first one of the plurality of agents on the solid tissue with a second effect of at least a second one of the plurality of agents on the solid tissue.

74. The method of claim 65 wherein the evaluating comprises, with respect to at least one of the plurality of agents, assessing at least one of efficacy, activity, and toxicity on the region of solid tissue.

75. The method of claim 65, comprising deselecting at least one of the plurality of agents based on the evaluating.

76. The method of claim 65, comprising selecting at least one of the plurality of agents based on the evaluating.

77. The method of claim 65, comprising prioritizing at least two of the plurality of agents based on the evaluating.

78. The method of claim 65, further comprising:

distributing the plurality of agents to a plurality of positions, each along a respective one of a plurality of parallel axes within a region of solid tissue within each of a plurality of subjects.

79. The method of claim 78 further comprising one of (i) selecting at least one of the plurality of agents based on the evaluating, (ii) deselecting at least one of the plurality of agents based on the evaluating, and (iii) prioritizing at least two of the plurality of agents based on the evaluating.

80. The method of claim 78 further comprising one of (i) selecting at least one of the plurality of subjects based on the evaluating, (ii) deselecting at least one of the plurality of subjects based on the evaluating, and (iii) prioritizing at least two of the plurality of subjects based on the evaluating.

81. The method of claim 75 wherein the evaluating comprises determining a level of altered physiologic state of the solid tissue near at least one of the plurality of parallel axes.

82. A fluid agent-delivering device comprising:

(i) a plurality of needles arranged in an array, each of said needles having, independently, one or a plurality of ports distributed along its length wherein at least one needle has said plurality of ports,

(ii) a plurality of reservoirs containing the fluid agent, each of said reservoirs being in fluid communication with a respective one of the plurality of needles, and

(iii) a plurality of plungers, a first end of each plunger being received in a respective one of the plurality of reservoirs and a second end of each plunger being depressable such that depressing each plunger results in injection of the fluid agent through the respective one of the plurality of needles.

83. A method for selective delivery of a fluid agent to a solid tissue, comprising:

(a) introducing a plurality of needles of a fluid agent-delivering device into the solid tissue; and

(b) administering the fluid agent into the solid tissue by injection through said needles.

84. The method of claim 83 wherein the solid tissue has been removed from a subject.

85. The method of claim 83 wherein the solid tissue is in a subject.

86. The method of claim 85 wherein the agent is delivered to the solid tissue in a therapeutically effective amount.

87. The method of claim 86 wherein outside the solid tissue the agent is either (i) undetectable, or (ii) if detectable outside the solid tissue, the agent is present at less than a minimal dose.

88. The method of claim 83 wherein the solid tissue comprises a tumor.

89. The method of claim 88 wherein the tumor is selected from the group consisting of a benign tumor and a malignant tumor.

90. The method of claim 88 wherein the tumor is selected from the group consisting of a primary tumor, an invasive tumor and a metastatic tumor.

91. The method of claim 88 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.

92. The method of claim 88 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.

93. The method of claim 83 wherein the 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

94. The method of claim 83 wherein the fluid agent comprises an agent that is selected from the group consisting of:

(a) a gene therapy agent;

(b) a chemotherapy agent;

(c) a small molecule;

(d) an antibody;

(e) a protein;

(f) one of a small interfering RNA and an encoding polynucleotide therefor;

(g) one of an antisense RNA and an encoding polynucleotide therefor;

(h) one of a ribozyme and an encoding polynucleotide therefor;

(i) a detectable label; and

(j) one of a therapeutic protein, polypeptide, and a peptidomimetic.

95. The method of claim 94 wherein the detectable label is selected from the group consisting of a radiolabel, a radio-opaque label, a fluorescent label, a colorimetric label, a dye, an enzymatic label, a GCMS tag, avidin, and biotin.

96. The method of claim 94 wherein the agent is selected from the group consisting of:

(i) a gene therapy agent that comprises at least one operably linked promoter,

(ii) a small interfering RNA-encoding polynucleotide that comprises at least one operably linked promoter;

(iii) an antisense RNA-encoding polynucleotide that comprises at least one operably linked promoter; and

(iv) a ribozyme-encoding polynucleotide that comprises at least one operably linked promoter.

97. The method of claim 96 wherein the operably linked promoter is selected from the group consisting of a constitutive promoter and a regulatable promoter.

98. The method of claim 97 wherein the regulatable promoter is selected from the group consisting of an inducible promoter, a tightly regulated promoter and a tissue-specific promoter.

99. A method for altering a physiologic state in a solid tissue, comprising:

(a) introducing a plurality of needles of a fluid agent-delivering device into the solid tissue; and

(b) administering the fluid agent into the solid tissue by injection through said needles.

100. A method for obtaining biological samples from a plurality of positions in a solid tissue, comprising:

(a) introducing a multiple needle device into the solid tissue, thereby placing a plurality of needles at a plurality of positions in the tissue; and

(b) generating negative pressure at a port of each needle of said multiple needle device under conditions and for a time sufficient to draw into said needles a plurality of biological samples from said plurality of positions in the tissue, and thereby obtaining biological samples from a plurality of positions in the tissue.

101. A method for obtaining biological samples from a plurality of positions along an axis in a solid tissue, comprising:

(a) introducing a multiple needle device into the solid tissue, thereby placing a plurality of needles at a plurality of positions in the tissue; and

(b) generating negative pressure at a plurality of ports located along a length of each needle of said multiple needle device under conditions and for a time sufficient to draw into said needles a plurality of biological samples from said plurality of positions in the tissue, and thereby obtaining biological samples from a plurality of positions along an axis in the tissue.

102. A method of screening subjects for eligibility to participate in a clinical trial of one or more agents, comprising:

(a) introducing one or more agents to a region of solid tissue in one or more subjects *in vivo* by distributing each of said agents to a plurality of positions along an axis within the region in each subject;

(b) removing the region of solid tissue from each of said subjects; and

(c) evaluating each region removed in (b) for an effect of each agent on the respective position along the axis within the region, wherein either (i) for any given agent or agents presence of a detectable effect of said agent or agents on the solid tissue region from the subject indicates eligibility of the subject for participation in a clinical trial of the agent or agents, (ii) for any given agent or agents absence of a detectable effect of said agent or agents on the solid tissue region from the subject indicates ineligibility of the subject for participation in a clinical trial of the agent or agents, or (iii) both (i) and (ii).

103. A method of rating a candidate agent for development into a therapeutic agent for treating a solid tumor, comprising:

(a) introducing one or more candidate agents to a region of a solid tumor of known tumor type in each one or more subjects having a tumor of the known tumor type, by distributing each of said candidate agents to a plurality of positions along an axis within the region in each subject;

(b) removing the region of solid tumor from each of said subjects; and

(c) comparing each region removed in (b) for an effect of each candidate agent on the respective position along the axis within the region, wherein an agent that results in a greater beneficial effect when introduced to the tumor receives a higher rating for development into a therapeutic agent for treating the solid tumor, and an agent that results in a lesser beneficial effect when introduced to the tumor receives a lower rating for development into a therapeutic agent for treating the solid tumor.

CLAIMS

1. A device for delivery of one or more agents into a solid tissue, comprising: a plurality of needles arranged in an array configured to deliver the one or more agents into the solid tissue along an axis of the plurality of needles; wherein the device is configured to deliver the one or more agents at less than a minimal dose required to produce a detectable effect in an adult, undetectable outside the solid tissue, or a therapeutically effective amount.

2. The device of claim 1, wherein each of the plurality of needles is configured to deliver the one or more agents in a column-shaped region coaxial with respect to the delivery axis.

3. The device of claim 1, wherein the device is configured to deliver a first agent to a plurality of positions within the solid tissue.

4. The device of claim 1, wherein the device is configured to deliver a plurality of different agents to a plurality of different positions within the solid tissue.

5. The device of claim 1, wherein the needles are close-ended.

6. The device of claim 1, wherein the device comprises needles with micro pits over their surfaces.

7. The device of claim 1, further comprising a linkage to a data processing system.

8. The device of claim 7, wherein the data processing system is in communicable connection with the needle array.

9. A device for delivery of one or more agents into a solid tissue, comprising: a plurality of needles arranged in an array configured to deliver the one or more agents into the solid tissue along an axis of the plurality of needles; wherein the device is configured for passive delivery of the one or more agents into the solid tissue.

10. A device for delivery of one or more agents into a solid tissue, comprising: a plurality of needles arranged in an array configured to deliver the one or more agents into the solid tissue along an axis of the plurality of needles; wherein an amount of agent in each of the plurality of needles is less than 1 μL per needle.

11. A device for delivery of one or more agents into a solid tissue, comprising: a plurality of needles arranged in an array configured to deliver the one or more agents into the solid tissue along an axis of the plurality of needles; wherein the device comprises more than one thousand needles.

12. A device for delivery of one or more agents into a solid tissue, comprising: a plurality of needles arranged in an array configured to deliver the one or more agents into the solid tissue along an axis of the plurality of needles; wherein the device comprises needles coated with nanowire.

13. A device for delivery of one or more agents into a solid tissue, comprising: a plurality of needles arranged in an array configured to deliver the one or more agents into the solid tissue along an axis of the plurality of needles; wherein the device comprises needles made from porous material.