shown effects on mitochondrial function through the swelling of mitochondrial matrices. Other teams explored combination of chemotherapies (e.g., temozolomide) with TTFields in GBM patients. Such research into combination interventions has uncovered other promising effects against glioblastoma.

SUMMARY OF THE INVENTION

[0004a] According to an aspect of the present invention, there is provided an apparatus for treating a tumor in a subject's body and facilitating delivery of a substance across cell membranes in the subject's body, the apparatus comprising:

an AC voltage generator capable of generating an alternating electric field at a first frequency between 50 kHz and 500 kHz and a second frequency between 50 kHz and 500 kHz, and having a control input, the second frequency being different from the first frequency, wherein the AC voltage generator is configured to output the alternating electric field at the first frequency when the control input is in a first state and at the second frequency when the control input is in a second state; and

a controller programmed to (a) place the control input in the second state so that the AC voltage generator outputs the alternating electric field at the second frequency, (b) accept a request to switch the alternating electric field to the first frequency, (c) upon receipt of the request, place the control input in the first state so that the AC voltage generator outputs the alternating electric field at the first frequency for an interval of time, and (d) after the interval of time has elapsed, place the control input in the second state so that the AC voltage generator outputs the alternating electric field at the second frequency.

[0005] There is disclosed a first method for delivering a substance across a cell membrane of a cell. The first method comprises applying an alternating electric field to the cell for a period of time, wherein application of the alternating electric field increases permeability of the cell membrane; and introducing the substance to a vicinity of the cell, wherein the increased permeability of the cell membrane enables the substance to cross the cell membrane.

[0006] In some instances of the first method, the cell is a cancer cell. In some instances of the first method, the cell is a glioblastoma cell. In some instances of the first method, the alternating electric is applied at a frequency of about 200 kHz. In some instances of the first method, the alternating electric field is applied at a frequency between 50 and 190 kHz. In some instances of the first method, the alternating electric field is applied at a frequency between 210 and 400 kHz. In some instances of the first method, the alternating electric field has a field strength of at least 1 V/cm.

[0007] In some instances of the first method, the cell is disposed in a body of a living subject, the alternating electric field is applied to the cell by applying an electric field to the subject's body, and the introducing comprises administering the substance to the subject. In these instances, the cell may be a cancer cell. In these instances, the cell may be a glioblastoma cell. In these instances, the alternating electric field may have a frequency between 50 and 190 kHz. In these instances, the alternating electric field may have a frequency between 210 and 400 kHz. In these instances, the alternating electric field may have a field strength of at least 1 V/cm RMS. In these instances, the alternating electric field may have a field strength between 1 and 4 V/cm RMS. In these instances, the step of introducing the substance may begin at a given time, and the step of applying the alternating electric field ends at least 12 hours after the given time. In these instances, the step of applying the alternating electric field may begin at least one hour before the given time. In these instances, the substance may have a molecular weight of at least 1.2 kDa. In these instances, the substance may have a molecular weight of at least 4 kDa. In these instances,

the substance may have a molecular weight of at least 20 kDa. In these instances, the substance may have at least one characteristic that ordinarily impedes the substance from crossing the cell membrane. In these instances, the cell may be a cancer cell that is innately resistant to treatment using the substance. In these instances, the cell may comprise a bacterium, and the substance comprises an antibiotic.

[0008] There is disclosed a second method for attacking cancer cells. The second method comprises applying a first alternating electric field at a first frequency to the cancer cells for a first period of time, wherein application of the first alternating electric field at the first frequency to the cancer cells for the first period of time increases permeability of cell membranes of the cancer cells; introducing a substance to the cancer cells, wherein the increased permeability of the cell membranes enables the substance to cross the cell membranes; and applying a second alternating electric field at a second frequency to the cancer cells for a second period of time, wherein the second frequency is different from the first frequency, and wherein the second alternating electric field at the second frequency reduces viability of the cancer cells.

[0009] In some instances of the second method, the cancer cells comprise glioblastoma cells, the first frequency is between 250 kHz and 350 kHz, and the second frequency is between 150 kHz and 250 kHz. In some instances of the second method, the cancer cells comprise uterine sarcoma cells, the first frequency is between 125 kHz and 175 kHz, and the second frequency is between 75 kHz and 125 kHz. In some instances of the second method, the cancer cells comprise breast adenocarcinoma cells, the first frequency is between 75 kHz and 175 kHz, and the second frequency is between 100 kHz and 300 kHz. In some instances of the second method, the step of introducing the substance begins at a given time, and the step of applying the first alternating electric field ends at least 12 hours after the given time. In some instances of the second method, the step of applying the first alternating electric field begins at least one hour before the given time. In some instances of the second method, the second period of time comprises a plurality of non-contiguous intervals of time during which the second alternating electric field at the second frequency is applied to the cancer cells, wherein the plurality of non-contiguous intervals of time collectively add up to at least one week.

[0010] In some instances of the second method, the cancer cells are disposed in a body of a living subject, the first alternating electric field is applied to the cancer cells by

applying a first alternating electric field to the subject's body, the second alternating electric field is applied to the cancer cells by applying a second alternating electric field to the subject's body, and the introducing comprises administering the substance to the subject. In some instances of the second method, the first alternating electric field has a field strength of at least 1 V/cm RMS. In some instances of the second method, the substance has a molecular weight of at least 1.2 kDa. In some instances of the second method, the substance has a molecular weight of at least 4 kDa. In some instances of the second method, the substance has a molecular weight of at least 20 kDa.

[0011] There is disclosed a third method for treating a tumor in a subject's body and delivering a substance across cell membranes in the subject's body. The third method comprises applying a first alternating electric field at a first frequency to the subject's body for a first period of time, wherein application of the first alternating electric field at the first frequency to the subject's body for the first period of time increases permeability of the cell membranes in the subject's body; administering the substance to the subject, wherein the increased permeability of the cell membranes enables the substance to cross the cell membranes; and applying a second alternating electric field at a second frequency to the subject's body for a second period of time that is at least one week long, wherein the second frequency is different from the first frequency, and wherein the second alternating electric field at the second frequency inhibits growth of the tumor.

[0012] In some instances of the third method, the tumor comprises a glioblastoma in the subject's brain, the first frequency is between 250 kHz and 350 kHz, and the second frequency is between 150 kHz and 250 kHz. In some instances of the third method, the second period of time comprises a plurality of non-contiguous intervals of time during which the second alternating electric field at the second frequency is applied to the subject's body, wherein the plurality of non-contiguous intervals of time collectively add up to at least one week. In some instances of the third method, the step of administering the substance begins at a given time, and the step of applying the first alternating electric field ends at least 12 hours after the given time. In some instances of the third method, the step of applying the first alternating electric field begins at least one hour before the given time.

[0013] In some instances of the third method, the substance has a molecular weight of at least 1.2 kDa. In some instances of the third method, the substance has a molecular weight

of at least 4 kDa. In some instances of the third method, the substance has a molecular weight of at least 20 kDa.

[0014] There is disclosed a first apparatus for treating a tumor in a subject's body and facilitating delivery of a substance across cell membranes in the subject's body. The first apparatus comprises an AC voltage generator capable of operating at a first frequency between 50 and 500 kHz and a second frequency between 50 and 500 kHz. Wherein the second frequency is different from the first frequency. The AC voltage generator has a control input, and the AC voltage generator is configured to output the first frequency when the control input is in a first state and to output the second frequency when the control input is in a second state. The first apparatus also comprises a controller programmed to (a) place the control input in the second state so that the AC voltage generator outputs the second frequency, (b) accept a request to switch to the first frequency, (c) upon receipt of the request, place the control input in the first state so that the AC voltage generator outputs the first frequency for an interval of time, and (d) after the interval of time has elapsed, place the control input in the second state so that the AC voltage generator outputs the second frequency.

[0015] Some embodiments of the first apparatus further comprise a set of electrodes configured for affixation to the subject's body; and wiring that connects an output of the AC voltage generator to the set of electrodes.

[0016] In some embodiments of the first apparatus, the first frequency is between 250 kHz and 350 kHz, and the second frequency is between 150 kHz and 250 kHz. In some embodiments of the first apparatus, the first frequency is between 125 kHz and 175 kHz, and the second frequency is between 75 kHz and 125 kHz. In some embodiments of the first apparatus, the first frequency is between 75 kHz and 175 kHz, and the second frequency is between 100 kHz and 300 kHz. In some embodiments of the first apparatus, the interval of time is at least 12 hours. In some embodiments of the first apparatus, the interval of time is between 12 and 72 hours. In some embodiments of the first apparatus, the controller is further programmed to, subsequent to the receipt of the request, switch the control input back and forth between the first state and the second state.

[0017] In some embodiments of the first apparatus, the AC voltage generator is capable of operating at at least one additional frequency between 50 and 500 kHz, and the

WHAT IS CLAIMED IS:

1. An apparatus for treating a tumor in a subject's body and facilitating delivery of a substance across cell membranes in the subject's body, the apparatus comprising:
an AC voltage generator capable of generating an alternating electric field at a first frequency between 50 kHz and 500 kHz and a second frequency between 50 kHz and 500 kHz, and having a control input, the second frequency being different from the first frequency, wherein the AC voltage generator is configured to output the alternating electric field at the first frequency when the control input is in a first state and at the second frequency when the control input is in a second state; and
a controller programmed to (a) place the control input in the second state so that the AC voltage generator outputs the alternating electric field at the second frequency, (b) accept a request to switch the alternating electric field to the first frequency, (c) upon receipt of the request, place the control input in the first state so that the AC voltage generator outputs the alternating electric field at the first frequency for an interval of time, and (d) after the interval of time has elapsed, place the control input in the second state so that the AC voltage generator outputs the alternating electric field at the second frequency.

2. The apparatus of claim 1, further comprising:
a set of electrodes configured for affixation to the subject's body; and
wiring that connects an output of the AC voltage generator to the set of electrodes.

3. The apparatus of claim 1, wherein the first frequency is between 250 kHz and 350 kHz, and the second frequency is between 150 kHz and 250 kHz.

4. The apparatus of claim 1, wherein the first frequency is between 125 kHz and 175 kHz, and the second frequency is between 75 kHz and 125 kHz.

5. The apparatus of claim 1, wherein the first frequency is between 75 kHz and 175 kHz, and the second frequency is between 100 kHz and 300 kHz.

6. The apparatus of claim 1, wherein the first frequency is between 50 kHz and 190 kHz.

7. The apparatus of claim 1, wherein the second frequency is between 210 kHz and 400

kHz.

8. The apparatus of claim 1, wherein the alternating electric field has a field strength of at least 1 V/cm RMS, optionally between 1 V/cm RMS and 4 V/cm RMS.

9. The apparatus of claim 1, wherein the cell is a cancer cell, optionally a glioblastoma cell, a uterine sarcoma cell or a breast adenocarcinoma cell.

10. The apparatus of claim 1, wherein the cell is a bacterium, and the substance comprises an antibiotic.

11. The apparatus of claim 1, wherein the interval of time is at least 12 hours, optionally between 12 hours and 72 hours.

12. The apparatus of claim 1, wherein the controller is further programmed to, subsequent to the receipt of the request, switch the control input back and forth between the first state and the second state.

13. The apparatus of claim 1, wherein the AC voltage generator is capable of generating the alternating electric field at at least one additional frequency between 50 kHz and 500 kHz and configured to output the at least one additional frequency when the control input is in at least one additional state, and the controller is programmed to cycle the control input through the second state and the at least one additional state prior to receipt of the request, and cycle the control input through the second state and the at least one additional state after the interval of time has elapsed.

14. The apparatus of claim 1, further comprising:
a user interface, wherein the request is accepted via the user interface; or
wherein the request is accepted via RF.

15. The apparatus of claim 1, wherein the substance has a molecular weight of at least 1.2 kDa, optionally at least 4 kDa, optionally at least 20 kDa.