SYSTEMS AND METHODS FOR COORDINATING MANUFACTURING OF CELLS FOR PATIENT-SPECIFIC IMMUNOTHERAPY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to US Provisional Application No. 63/013,942, filed on April 22, 2020, US Provisional Application No. 63/155,711, filed March 2, 2021, and US Provisional Application No. 63/159,806, filed March 11, 2021, each of which is incorporated herein by reference in its entirety for all purposes.

BACKGROUND

[0002] Treatment of bulky, refractory cancers using adoptive transfer of tumor infiltrating lymphocytes (TILs) represents a powerful approach to therapy for patients with poor prognoses. Gattinoni, *et al.*, *Nat. Rev. Immunol.* **2006,** *6,* 383-393. A large number of TILs are required for successful immunotherapy, and a robust and reliable process is needed for commercialization. This has been a challenge to achieve because of technical, logistical, and regulatory issues with cell expansion. IL-2-based TIL expansion followed by a "rapid expansion process" (REP) has become a preferred method for TIL expansion because of its speed and efficiency. Dudley, *et al.*, *Science* **2002,** *298,* 850-54; Dudley, *et al.*, *J. Clin. Oncol.* **2005,** *23,* 2346-57; Dudley, *et al.*, *J. Clin. Oncol.* **2008**, *26,* 5233-39; Riddell, *et al.*, *Science* **1992,** *257,* 238-41; Dudley, *et al.*, *J. Immunother.* **2003**, *26,* 332-42. REP can result in a 1,000-fold expansion of TILs over a 14-day period, although it requires a large excess (*e.g.*, 200-fold) of irradiated allogeneic peripheral blood mononuclear cells (PBMCs, also known as mononuclear cells (MNCs)), often from multiple donors, as feeder cells, as well as anti-CD3 antibody (OKT3) and high doses of IL-2. Dudley, *et al., J. Immunother.* **2003,** *26,* 332-42. TILs that have undergone an REP procedure have produced successful adoptive cell therapy following host immunosuppression in patients with melanoma.

SUMMARY

[0002a] In one aspect, the present disclosure refers to a method of manufacturing a cell therapy product for treating cancer in a patient, the method comprising:

initiating expansion of the cell therapy product from at least a portion of a tumor or a population of cells obtained from the patient using a multi-step cell expansion process, based on a cell order request to manufacture the cell therapy product, a preliminary schedule of patient

treatment events for treating the patient with the cell therapy product, and a selected manufacturing slot at a manufacturing facility, wherein the manufacturing slot is selected from a plurality of available manufacturing slots based on the preliminary schedule of patient treatment events;

performing quality control assays to determine acceptance parameters at each of a plurality of time points during the multi-step cell expansion process, wherein the acceptance parameters comprise one or more of viability, sterility, cell count, mycoplasma count, CD3 count, a result of an endotoxin assay, or a result of a Gram strain assay;

determining, during the manufacturing of the cell therapy product, whether the acceptance parameters determined at each of the plurality of time points meet the acceptance criteria associated with the time point; and

in response to a determination that the acceptance parameters meet the acceptance criteria at each of the plurality of time points, continuing the cell expansion process to manufacture the cell therapy product.

In another aspect, the present disclosure refers to a system for coordinating manufacturing of a cell therapy product for treating cancer, the system comprising:

i) a hospital-side subsystem comprising at least one computing device and configured to:

receive and transmit patient information and a cell order request for manufacturing the cell therapy product from a population of cells obtained from a tumor sample from a patient, the patient information including a patient-specific identifier, and the cell order request including a cell order identifier, and

determine a preliminary schedule for patient treatment events based on an estimated completion date for obtaining of the cell therapy product manufactured by and received from a manufacturing facility;

ii) a manufacturing subsystem comprising at least one computing device and configured to use in a multi-step cell expansion process at the manufacturing facility, wherein the multi-step cell expansion process comprises:

initiating expansion of the cell therapy product from at least a portion of the population of cells obtained from the tumor sample, based on the cell order request, the preliminary

schedule for patient treatment events, and a selected manufacturing slot at the manufacturing facility;

performing quality control assays to determine acceptance parameters at each of a plurality of time points during the multi-step cell expansion process, wherein the acceptance parameters comprise one or more of viability, sterility, cell count, mycoplasma count, CD3 count, a result of an endotoxin assay, or a result of a Gram strain assay;

determining whether the acceptance parameters determined at each of the plurality of time points meet acceptance criteria associated with the time point; and

in response to a determination that the acceptance parameters meet the acceptance criteria at each of the plurality of time points, continuing the cell expansion process to manufacture the cell therapy product; and

iii) a logistics subsystem comprising at least one computing device and configured to:

transmit a shipping request to a logistics facility based on a shipping schedule received from the hospital-side subsystem and/or the manufacturing subsystem.

In another aspect, the present disclosure refers to a system for coordinating manufacturing of a cell therapy product for treating cancer, the system comprising:

i) a manufacturing subsystem comprising at least one computing device and configured to use in a multi-step cell expansion process at a manufacturing facility, wherein the multi-step cell expansion process comprises:

initiating expansion of the cell therapy product from at least a portion of a population of cells obtained from a tumor sample obtained from a patient at a hospital facility, based on a cell order request to manufacture the cell therapy product, a preliminary schedule of patient treatment events for treating the patient with the cell therapy product, and a selected manufacturing slot at the manufacturing facility, wherein the manufacturing slot is selected from a plurality of available manufacturing slots based on the preliminary schedule of patient treatment events;

performing quality control assays to determine acceptance parameters at each of a plurality of time points during the multi-step cell expansion process, wherein the acceptance parameters comprise one or more of viability, sterility, cell count, mycoplasma count, CD3 count, a result of an endotoxin assay, or a result of a Gram strain assay;

determining whether the acceptance parameters determined at each of the plurality of time points meet acceptance criteria associated with the time point; and

in response to a determination that the acceptance parameters meet the acceptance criteria at each of the plurality of time points, continuing the cell expansion process to manufacture the cell therapy product; and

ii) a logistics subsystem comprising at least one computing device and configured to:

transmit a shipping request to a logistics facility based on a shipping schedule received from the manufacturing subsystem.

In one example, the present disclosure refers to a method for manufacturing a cell therapy product comprising tumor infiltrating lymphocytes (TILs) to be used in a composition for treating a patient having cancer, the method comprising:

receiving, at a computing device, a request for manufacturing the cell therapy product, from at least a portion of a solid tumor obtained from the patient or a first population of cells obtained from the solid tumor, using a selected multi-step cell expansion process, the request including acceptance criteria for manufactured cell therapy product at each of a plurality of steps during the selected multi-step cell expansion process;

generating, by the computing device, a container label based on the request, the container label comprising information associated with:

(a) a manufacturing order received from a treatment facility requesting the cell therapy product, including an order-specific identifier,

(b) the patient, including a patient-specific identifier,

(c) the treatment facility requesting the manufacturing of the cell therapy product,

(d) the selected multi-step cell expansion process; and

(e) a manufacturing facility where the cell therapy product is to be manufactured;

determining, by the computing device, a schedule for manufacturing the cell therapy product at the manufacturing facility based on

(i) a time of receipt of the solid tumor or the first population of cells and

(ii) the selected multi-step cell expansion process;

generating, by the computing device, a manufacturing label to be affixed to a manufacturing container to be used during the selected multi-step cell expansion process, the manufacturing label comprising information associated with:

(a) the manufacturing order, including the order-specific identifier,

(b) the patient, including the patient-specific identifier,

(c) the selected multi-step cell expansion process or a step thereof and

(f) quality of manufactured cell therapy product;

initiating the selected multi-step cell expansion process to manufacture the cell therapy product in accordance with the schedule;

performing quality control assays to determine acceptance parameters at each of a plurality of time points during the selected multi-step cell expansion process;

at each of the plurality of time points generating, by the computing device, a respective updated manufacturing label, to be affixed to the manufacturing container, corresponding to a respective one of the plurality of time points, the updated manufacturing label comprising information associated with

(a) the manufacturing order, including the order-specific identifier,

(b) the patient, including the patient identifier,

(c) the selected multi-step cell expansion process and

(ee) updated information associated with quality of manufactured cell therapy product comprising the determined acceptance parameters at a corresponding time point;

determining an adjusted schedule, by the computing device, for manufacturing the cell therapy product based on whether the acceptance parameters at a given time point read from the updated manufacturing label meet the acceptance criteria at the given time point; and

completing the selected multi-step cell expansion process in accordance with the adjusted schedule to manufacture the cell therapy product.

[0002b] In one example, the present disclosure refers to a method for manufacturing a cell therapy product comprising tumor infiltrating lymphocytes (TILs) for treatment of cancer, the method comprising:

receiving, at a computing device, an indication that a solid tumor obtained from a patient having the cancer or a first population of cells comprising TILs obtained from the solid tumor obtained from the patient has been received at a manufacturing facility for manufacturing the cell therapy product using a selected multi-step cell expansion process;

generating, by the computing device, a manufacturing label to be affixed to a manufacturing container to be used during a multi-step cell expansion process for manufacturing the cell therapy product from at least a portion of the obtained solid tumor or the first population of cells, the manufacturing label comprising information associated with:

(a) a manufacturing order received from a treatment facility requesting the cell therapy product, including an order-specific identifier,

(b) the patient, including a patient-specific identifier,

(c) the selected multi-step cell expansion process and

(d) quality of manufactured cell therapy product;

initiating the multi-step cell expansion process to manufacture the cell therapy product;

performing a quality control assay to determine acceptance parameters for the manufactured cell therapy product at each of a plurality of time points during the selected multi-step cell expansion process;

receiving, at the computing device, the acceptance parameters for the manufactured cell therapy product at each of the plurality of time points;

reading, by the computing device, the manufacturing label at each of the plurality of time points; and

for each step of the multi-step cell expansion process, generating, by the computing device, a warning signal when:

information relating to the patient on the manufacturing label for the step does not match the information relating to the patient on the manufacturing label for an immediately preceding manufacturing step, or

acceptance parameters on the manufacturing label for a given time point in the selected multi-step cell expansion process do not meet acceptance criteria for the given time point in the selected multi-step cell expansion process.

BRIEF DESCRIPTION OF DRAWINGS

[0003] FIG. 1 schematically depicts various stages in a treatment of a patient using adoptive cell therapy using TILs including various steps for manufacturing allogenic TILs.

[0004] FIG. 2A shows the timeline for a GEN 3 process for TIL manufacturing.

1. **CLAIMS**

What is claimed is:

1. A method of manufacturing a cell therapy product for treating cancer in a patient, the method comprising:

initiating expansion of the cell therapy product from at least a portion of a tumor or a population of cells obtained from the patient using a multi-step cell expansion process, based on a cell order request to manufacture the cell therapy product, a preliminary schedule of patient treatment events for treating the patient with the cell therapy product, and a selected manufacturing slot at a manufacturing facility, wherein the manufacturing slot is selected from a plurality of available manufacturing slots based on the preliminary schedule of patient treatment events;

performing quality control assays to determine acceptance parameters at each of a plurality of time points during the multi-step cell expansion process, wherein the acceptance parameters comprise one or more of viability, sterility, cell count, mycoplasma count, CD3 count, a result of an endotoxin assay, or a result of a Gram strain assay;

determining, during the manufacturing of the cell therapy product, whether the acceptance parameters determined at each of the plurality of time points meet the acceptance criteria associated with the time point; and

in response to a determination that the acceptance parameters meet the acceptance criteria at each of the plurality of time points, continuing the cell expansion process to manufacture the cell therapy product.

2. The method of claim 1, wherein the patient treatment events include one or more of an in-patient stay time period, resection date, lymphodepletion date, infusion date for infusing the patient with the cell therapy product, or IL-2 treatment date.

3. The method of claim 1, wherein the plurality of time points comprises a first time point and a second time point subsequent to the first time point, and wherein the method further comprises:

in response to a determination that the acceptance parameters do not meet the acceptance criteria at the second time point because of reasons other than contamination, determining whether re-performing the multi-step cell expansion process is feasible from the first time point based on the acceptance parameters at the second time point; and

in response to a determination that re-performing the multi-step cell expansion process is feasible, re-performing the multi-step cell expansion process from the first time point to manufacture the cell therapy product from at least some of the cell therapy product obtained at the second time point,

estimating a time of completion of the multi-step cell expansion process following the re-performing, and

rescheduling the patient treatment events and completing the multi-step cell expansion process from the first time point,

wherein the rescheduling of the patient treatment events is performed based on the estimated time of completion of the multi-step cell expansion process and a timing of patient treatment events prior to or subsequent to an infusion of the expanded cell therapy product in the patient.

4. The method of claim 3, wherein a cell order identifier and a patient-specific identifier associated with the patient and the cell order request is generated, by a computing device, and wherein the cell order identifier and the patient-specific identifier define a chain of custody (COC) and a chain of identity (COI), respectively, for the cell therapy product.

5. The method of claim 4, further comprising:

transmitting, upon rescheduling the patient treatment events, to a hospital-side interface of the computer device an updated schedule for the patient treatment events associated with the patient-specific identifier; and

transmitting, to a logistics interface, a pick-up order associated with the patient-specific identifier based on an estimated time of completion of manufacturing of the cell therapy product.

6. The method of claim 4, further comprising:

upon determination that re-performing the multi-step cell expansion process from the first time point is feasible, disassociating, by the computing device, the cell order identifier from the patient-specific identifier, and

generating, by the computing device, a new cell order identifier associated with the cell order request and associating the new cell order identifier with the patient-specific identifier.

7. The method of claim 4, further comprising automatically generating, by the computing device, a shipping label for a container for the obtained tumor or the population of cells, the shipping label comprising the patient-specific identifier, the cell order request, the selected available manufacturing slot and the manufacturing facility corresponding to the selected available manufacturing slot.

8. The method of claim 7, further comprising

automatically generating, by the computing device, a manufacturing label for the container for the obtained tumor or the population of cells,

wherein the manufacturing label comprises a time point corresponding to the manufacturing process being used for manufacturing the cell therapy product when the manufacturing label is generated, a container-identifying bar code, the patient-specific identifier, manufacturing steps completed at the time point, acceptance parameters associated with the completed processes, and/or the manufacturing process being performed at the time point, wherein the manufacturing label is updated at each of the plurality of time points, and wherein an updated manufacturing label comprises updated information associated with quality of manufactured cell therapy product, the updated information comprising the acceptance parameters at the time point.

9. The method of claim 8, further comprising:

providing, by the computing device, a warning signal if:

information relating to the patient on the updated manufacturing label for a given manufacturing step does not match the information relating to the patient on the manufacturing label for an immediately preceding manufacturing step, or

acceptance parameters on the updated manufacturing label for a given time point in the multi-step cell expansion process do not meet acceptance criteria for the given time point in the multi-step cell expansion process.

10. The method of claim 8, wherein the manufacturing label comprises a barcode encoding the information associated with the patient, the manufacturing process and quality of manufactured cell therapy product.

11. The method of claim 4, wherein the cell order request is received from a hospital, and the method further comprises transmitting, upon receiving the cell order request, a confirmation, including one or both of the patient-specific identifier and the cell order identifier, to the hospital that the cell order request associated with the patient has been received.

12. The method of claim 1, further comprising:
shipping the manufactured cell therapy product to a hospital facility to treat the patient.

13. The method of claim 1, wherein the multi-step cell expansion process includes culturing the cell therapy product in a single closed container bioreactor.

14. The method of claim 1, wherein the multi-step cell expansion process comprises a rapid expansion step, and wherein the method further comprises:

determining whether the acceptance parameters obtained prior to the rapid expansion step meet the corresponding acceptance criteria; and

in response to a determination that the acceptance parameters obtained prior to the rapid expansion step meet the corresponding acceptance criteria, scheduling a lymphodepletion date at a date prior to the completion of the multi-step cell expansion process, scheduling an infusion date for treating the patient with the manufactured cell therapy product at a date following the completion of the multi-step cell expansion process, and/or scheduling an IL-2 treatment date following the infusion date.

15. The method of claim 1, wherein the cell therapy product comprises tumor infiltrating lymphocytes (TILs).

16. The method of claim 15, wherein the multi-step cell expansion process comprises steps of:

(a) providing a first population of TILs obtained from the tumor or the population of cells from the patient;

(b) performing a first expansion by culturing the first population of cells in a cell culture medium comprising IL-2 to produce a second population of cells, wherein the first expansion is performed in a closed container providing a first gas-permeable surface area, and wherein the first expansion is performed for about 3-14 days to obtain the second population of cells;

(c) performing a second expansion by culturing the second population of cells in a cell culture medium comprising OKT-3 and antigen presenting cells (APCs), optionally further comprising IL-2, to produce a third population of cells, wherein the second expansion is performed for about 7-14 days to obtain the third population of cells, wherein the second expansion is performed in a closed container providing a second gas-permeable surface area, and wherein the transition from step (b) to step (c) occurs without opening the system;

(d) harvesting the third population of cells obtained from step (c), wherein the transition from step (c) to step (d) occurs without opening the system;

(e) optionally transferring the harvested cell population from step (d) to an infusion bag, wherein the optional transfer from step (d) to (e) occurs without opening the system; and

(f) optionally cryopreserving the harvested cell population with a cryopreservation process.

17. The method of claim 16, wherein the third population of cells is a therapeutic population of cells which comprises an increased subpopulation of effector T cells and/or central memory T cells relative to the second population of cells.

18. The method of claim 17, wherein the effector T-cells and/or central memory T-cells in the third population of TILs exhibit increased CD57 expression and decreased CD56 expression.

19. The method of claim 16, wherein the first population of TILs is obtained from a tumor sample obtained from the patient through one or more of surgical resection, needle biopsy, core biopsy, or small biopsy.

20. A system for coordinating manufacturing of a cell therapy product for treating cancer, the system comprising:

i) a hospital-side subsystem comprising at least one computing device and configured to:

receive and transmit patient information and a cell order request for manufacturing the cell therapy product from a population of cells obtained from a tumor sample from a patient, the patient information including a patient-specific identifier, and the cell order request including a cell order identifier, and

determine a preliminary schedule for patient treatment events based on an estimated completion date for obtaining of the cell therapy product manufactured by and received from a manufacturing facility;

ii) a manufacturing subsystem comprising at least one computing device and configured to use in a multi-step cell expansion process at the manufacturing facility, wherein the multi-step cell expansion process comprises:

initiating expansion of the cell therapy product from at least a portion of the population of cells obtained from the tumor sample, based on the cell order request, the preliminary schedule for patient treatment events, and a selected manufacturing slot at the manufacturing facility;

performing quality control assays to determine acceptance parameters at each of a plurality of time points during the multi-step cell expansion process, wherein the acceptance parameters comprise one or more of viability, sterility, cell count, mycoplasma count, CD3 count, a result of an endotoxin assay, or a result of a Gram strain assay;

determining whether the acceptance parameters determined at each of the plurality of time points meet acceptance criteria associated with the time point; and

in response to a determination that the acceptance parameters meet the acceptance criteria at each of the plurality of time points, continuing the cell expansion process to manufacture the cell therapy product; and

iii) a logistics subsystem comprising at least one computing device and configured to:

transmit a shipping request to a logistics facility based on a shipping schedule received from the hospital-side subsystem and/or the manufacturing subsystem.

21. A system for coordinating manufacturing of a cell therapy product for treating cancer, the system comprising:

i) a manufacturing subsystem comprising at least one computing device and configured to use in a multi-step cell expansion process at a manufacturing facility, wherein the multi-step cell expansion process comprises:

initiating expansion of the cell therapy product from at least a portion of a population of cells obtained from a tumor sample obtained from a patient at a hospital facility, based on a cell order request to manufacture the cell therapy product, a preliminary schedule of patient treatment events for treating the patient with the cell therapy product, and a selected manufacturing slot at the manufacturing facility, wherein the manufacturing slot is selected from a plurality of available manufacturing slots based on the preliminary schedule of patient treatment events;

performing quality control assays to determine acceptance parameters at each of a plurality of time points during the multi-step cell expansion process, wherein the acceptance parameters comprise one or more of viability, sterility, cell count, mycoplasma count, CD3 count, a result of an endotoxin assay, or a result of a Gram strain assay;

determining whether the acceptance parameters determined at each of the plurality of time points meet acceptance criteria associated with the time point; and

in response to a determination that the acceptance parameters meet the acceptance criteria at each of the plurality of time points, continuing the cell expansion process to manufacture the cell therapy product; and

ii) a logistics subsystem comprising at least one computing device and configured to:

transmit a shipping request to a logistics facility based on a shipping schedule received from the manufacturing subsystem.

22. The system of claim 20 or 21, wherein the patient treatment events include one or more of an in-patient stay time period, resection date, lymphodepletion date, infusion date for infusing the patient with the cell therapy product, or IL-2 treatment date.

23. The system of any one of claims 20 to 22, wherein the manufacturing subsystem is further configured to:

prior to the multi-step cell expansion process, generate a manufacturing label for a manufacturing container to be used in the multi-step cell expansion process, the manufacturing label comprising the cell order identifier, the patient-specific identifier, and information associated with the process for manufacturing and quality of the cell therapy product,

during the multi-step cell expansion process, update the manufacturing label corresponding to each of the plurality of time points comprising updated information associated with quality of the cell therapy product, the updated information being based on whether the acceptance parameters meet the acceptance criteria at each of the plurality of time points,

read the updated manufacturing label at each of the plurality of time points, and

verify a chain of custody and a chain of identity based on the cell order identifier and the patient-specific identifier on the manufacturing label at each of the plurality of time points.

24. The system of claim 23, wherein the manufacturing subsystem is further configured to: generate a warning signal if:

the patient-specific identifier on the updated manufacturing label for a subsequent manufacturing step does not match the patient-specific identifier on the manufacturing label for an immediately preceding manufacturing step, or

the acceptance parameters on the updated manufacturing label for a given time point in the multi-step cell expansion process do not meet the acceptance criteria for that time point.

25. The system of any one of claims 20 to 24, wherein the plurality of time points comprises a first time point and a second time point subsequent to the first time point, and wherein the multi-step cell expansion process further comprises:

in response to a determination that the acceptance parameters do not meet the acceptance criteria at the second time point because of reasons other than contamination, determining whether re-performing the multi-step cell expansion process is feasible from the first time point based on the acceptance parameters at the second time point;

in response to a determination that re-performing the multi-step cell expansion process is feasible, re-performing the multi-step cell expansion process from the first time point to manufacture the cell therapy product from at least some of the cell therapy product obtained at the second time point; and

estimating a time of completion of the multi-step cell expansion process following the re-performing.

26. The system of claim 25, wherein either the manufacturing subsystem or the hospital-side subsystem is further configured to

reschedule the patient treatment events, based on the estimated time of completion of the multi-step cell expansion process and a timing of the patient treatment events.

27. The system of claim 26, wherein the multi-step cell expansion process further comprises:

transmitting the rescheduled patient treatment events to the hospital-side subsystem; and

transmitting, to the logistics subsystem, a pick-up order for the manufactured cell therapy product, based on the rescheduled patient treatment events.

28. The system of claim 25, wherein the multi-step cell expansion process further comprises:

upon determination that re-performing the multi-step cell expansion process from the first time point is feasible, disassociating, by the computing device, the cell order identifier from the patient-specific identifier, and

generating a new cell order identifier associated with the cell order request and associating the new cell order identifier with the patient-specific identifier.

29. The system of any one of claims 20 to 28, wherein the multi-step cell expansion process is performed in a single closed container bioreactor.

30. The system of any one of claims 20 to 29, wherein the cell therapy product comprises tumor infiltrating lymphocytes (TILs).