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 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 aspect, 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 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.

2. The method of claim 1, further comprising, for each step of the selected multi-step cell expansion process, providing, by the computing device, a warning signal when:

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

acceptance parameters on the updated 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,

wherein the acceptance parameters comprise one or more of viability, sterility, cell count, mycoplasma count, CD3 count, a result of an endotoxin assay, and a result of a Gram stain assay.

3. The method of claim 1, wherein the selected multi-step cell expansion process includes culturing the TILs obtained from the solid tumor or the first population of cells in a closed container bioreactor.

4. The method of claim 1, wherein the manufacturing label comprises a barcode encoding the information associated with the patient, the selected multi-step cell expansion process and quality of manufactured cell therapy product.

5. The method of claim 1, wherein determining the schedule for manufacturing the cell therapy product comprises scheduling a set of dates corresponding to a plurality of time points, including a first time point and a second time point subsequent to the first time point, for determining whether acceptance parameters for the manufactured cell therapy product meet the acceptance criteria during the selected multi-step cell expansion process to manufacture the cell therapy product depending on the selected multi-step cell expansion process and when the manufacturing order is received at the manufacturing facility.

6. The method of claim 1, further comprising receiving courier status information via the computing device;

in response to receiving the courier status information, determining shipping schedule for shipping the manufactured cell therapy product based on the adjusted schedule of manufacturing, and

generating a shipping label for a shipping container containing the manufactured cell therapy product.

7. The method of claim 6, further comprising transmitting, by the computing device, a shipping request to a logistics facility based on the determined shipping schedule.

8. The method of claim 1, further comprising:

upon determining that the acceptance parameters for the manufactured cell therapy product meet the acceptance criteria, by the computing device, determining a completion date for the manufacturing of the cell therapy product;

generating, by the computing device, a schedule for patient treatment events corresponding to a use of the cell therapy product for treating a patient based on the completion date;

transmitting, by the computing device, to a logistics interface, a pick-up order based on the completion date; and

transmitting, by the computing device, to a hospital-side interface, the schedule for the patient treatment events.

9. The method of claim 1, wherein the manufacturing label further comprises a given time point corresponding to a given step of the selected multi-step cell expansion process when the manufacturing label is generated, a container-identifying code, steps completed at the given time point, acceptance parameters associated with the completed steps, and a step to be performed at or after the given time point.

10. The method of claim 1, wherein the manufacturing label comprises a graphical identification code encoding

(a) a manufacturing order received from a treatment facility requesting the cell therapy product,

(b) the patient, including a patient identifier,

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

(d) quality of manufactured cell therapy product,

the graphical identification code being one of a 1-dimensional barcode and a 2-dimensional barcode.

11. The method of claim 1, further comprising generating a contingent shipping label for a shipping container containing the cell therapy product before performing a final quality

control assay, the contingent shipping label being indicative that the cell therapy product is not releasable unless a result of the final quality control assay indicates that the acceptance parameters meet acceptance criteria.

12. 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.

13. The method of claim 12, wherein the acceptance parameters comprise one or more of viability, sterility, cell count, mycoplasma count, CD3 count, a result of an endotoxin assay, and a result of a Gram stain assay.

14. The method of claim 12, further comprising generating, by the computing device, an updated manufacturing label corresponding to each of the plurality of time points, the updated manufacturing label further comprising updated information associated with quality of manufactured cell therapy product, the updated information comprising the acceptance parameters at a corresponding time point.

15. The method of claim 12, wherein the warning signal comprises:

when information relating to the patient on the manufacturing label for the manufacturing step does not match the information relating to the patient on the manufacturing label for the immediately preceding manufacturing step, a prevention signal preventing performance of subsequent steps in the multi-step cell expansion process.

16. The method of claim 12, wherein the warning signal comprises:

if 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 that time point in the selected multi-step cell expansion process, an alert signal indicating that the acceptance criteria for the given time point are not met.

17. The method of claim 16, wherein the alert signal causes the computing device to generate an updated manufacturing label comprising updated information associated with quality of manufactured cell therapy product, the updated information comprising the acceptance parameters at the given time point.

18. The method of claim 17, further comprising reading the updated manufacturing label and determining, based on the updated information, whether additional processing of the manufactured cell therapy product can be performed to meet the acceptance criteria at that time point.

19. The method of claim 18, further comprising controlling, by the computing device, the multi-step cell expansion process to enable the additional processing of the manufactured cell therapy product to meet the acceptance criteria at the given time point.