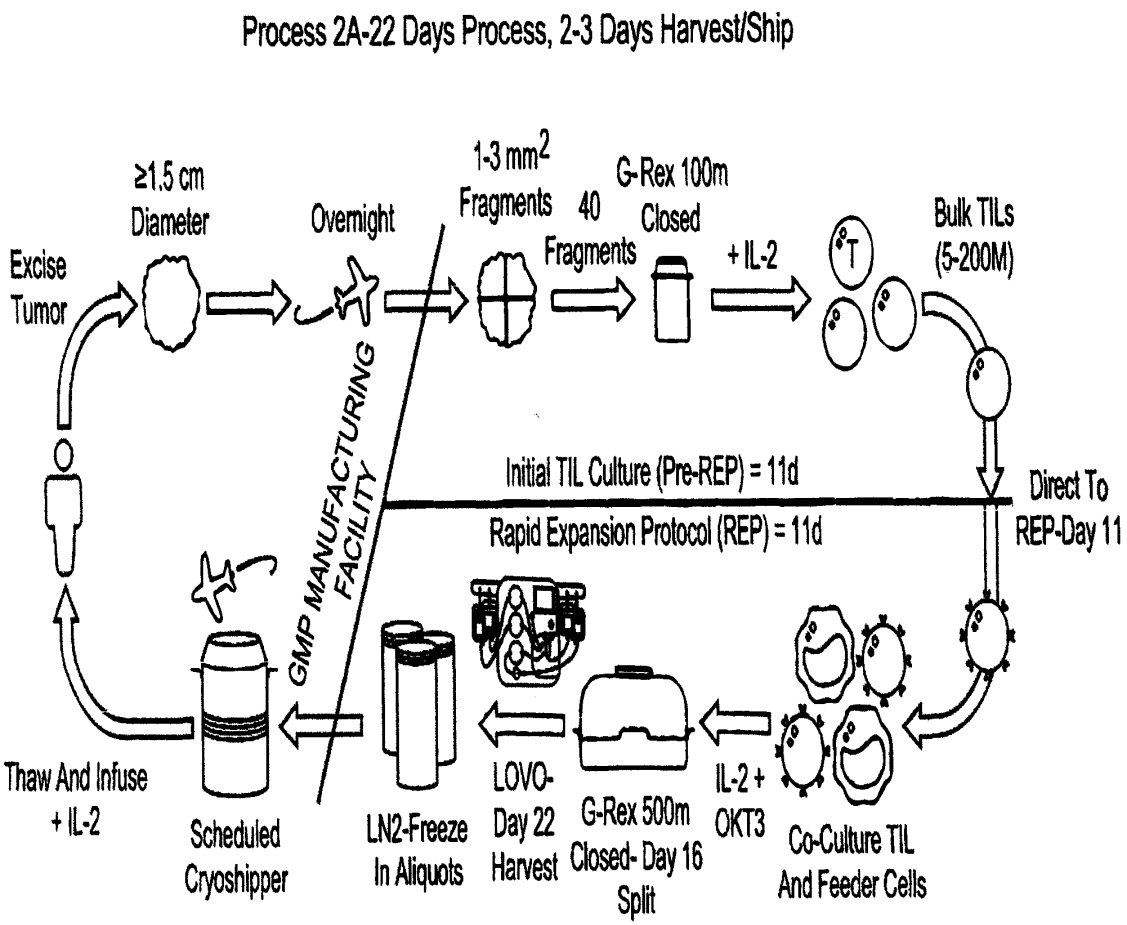

Process 2A-22 Days Process, 2-3 Days Harvest/Ship
≥1.5 cm Diameter
Excise Tumor
Overnight
1-3 mm2 Fragments
40 Fragments
G-Rex 100m Closed
+ IL-2
Bulk TILs (5-200M)
GMP MANUFACTURING FACILITY
Initial TIL Culture (Pre-REP) = 11d
Rapid Expansion Protocol (REP) = 11d
Direct To REP-Day 11
Thaw And Infuse + IL-2
Scheduled Cryoshipper
LN2-Freeze In Aliquots
LOVO-Day 22 Harvest
G-Rex 500m Closed- Day 16 Split
IL-2 + OKT3
Co-Culture TIL And Feeder Cells

Figure 1

Process Development

Step	Current Process-1C	New Process-2A	Impact
1	4 Fragments/10 G-Rex 10-21 Days	40 Fragments/1-G-Rex 100 CS- (x2?) 11 Days	Increases Tumor Sample/Container, Shortens Culture, Reduces Steps, Amenable To Closed System
2	PreREP Freeze-> Testing -> Thaw- ~Day 27- >40e6TIL	Direct To REP- Day 11- <200e6	Shorten Process, Reduces Steps, Eliminates Testing
3	36 G-Rex 100-~Day 30 >5e6TIL - Split ~Day 36	4-5 G-Rex 500CS-TIL- Split Day 16	Reduces Steps, Closed System, Shorter REP
4	Harvest Day ~43+ Harvesting By Centrifugation	Harvest Day 22 LOVO-Automated Cell Washer	Reduces Steps, Automated, Closed System
5	Fresh Product-Hypothermosol-Single Infusion Bag	Cryopreserved Product-CS10 In LN_2, Multiple Aliquots	Shipping Flexibility, Patient Scheduling, Easier Release Testing, Global Trials
6	43+ Day Process Time	22 Day Process Time	Turnaround To Patient, Clean Room Throughput, COGs

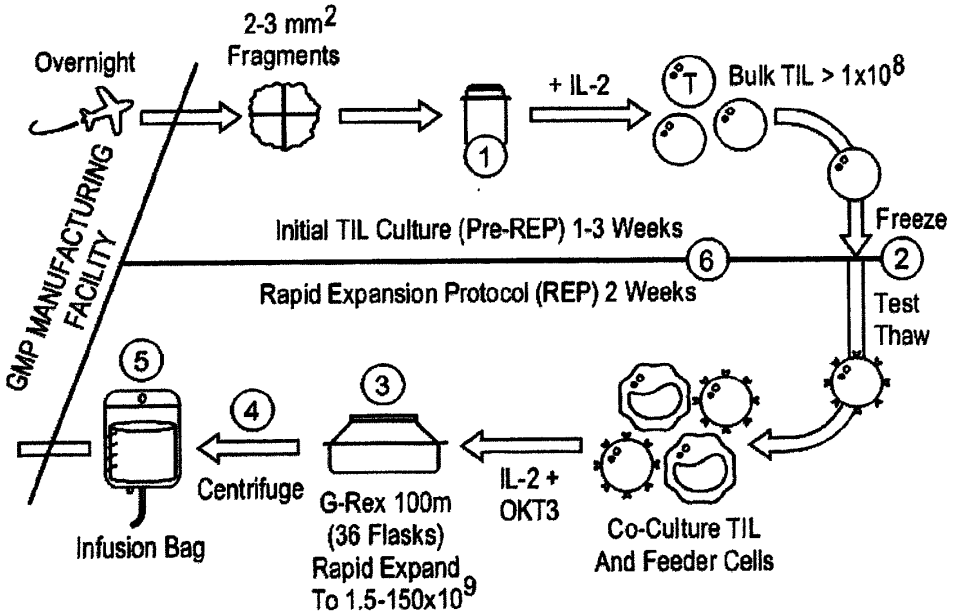


Figure 2

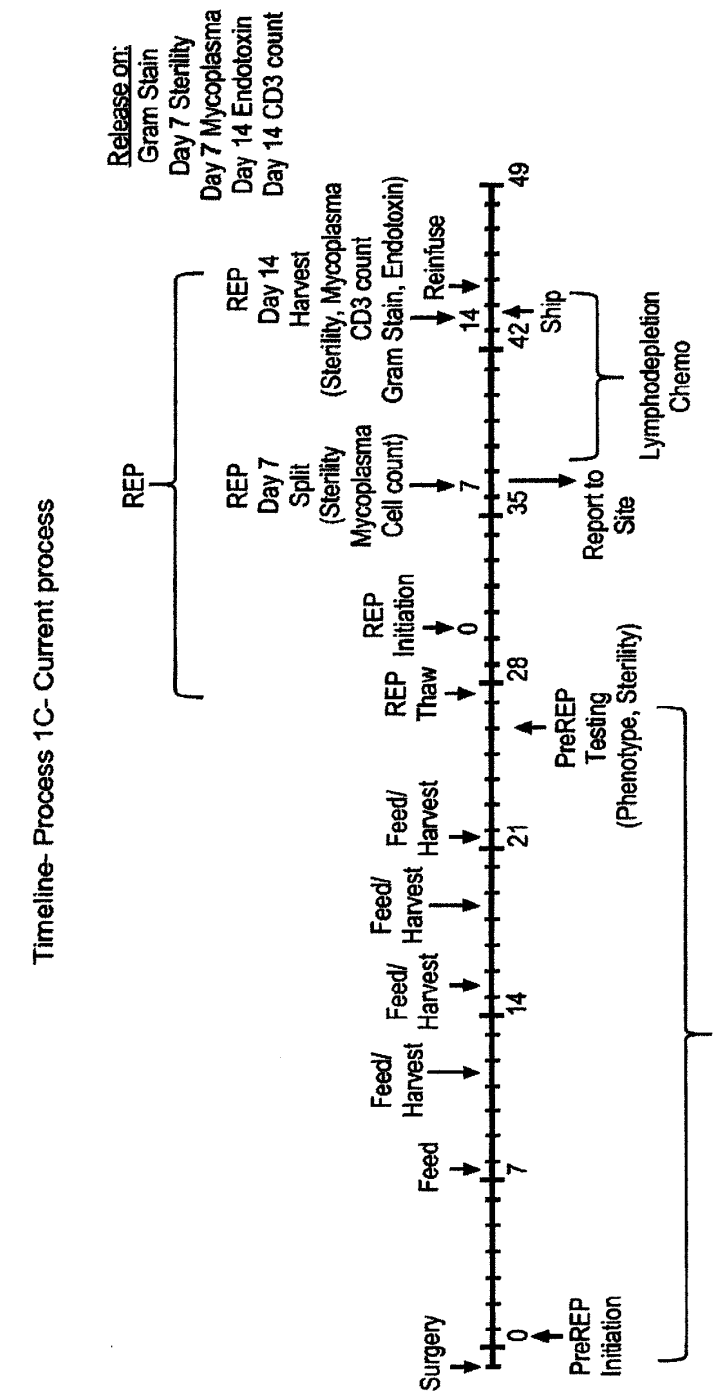

Timeline- Process 1C- Current process
Surgery
PreREP Initiation
0
Feed
7
Feed/ Harvest
Feed/ Harvest
14
Feed/ Harvest
Feed/ Harvest
21
PreREP Testing (Phenotype, Sterility)
28
REP Thaw
REP Initiation
0
REP Day 7 Split (Sterility Mycoplasma Cell count)
7
Report to Site
35
Lymphodepletion Chemo
REP Day 14 Harvest (Sterility, Mycoplasma CD3 count Gram Stain, Endotoxin)
Reinfuse
14
42
Ship
49
REP
Release on:
Gram Stain
Day 7 Sterility
Day 7 Mycoplasma
Day 14 Endotoxin
Day 14 CD3 count
PreREP

Figure 3

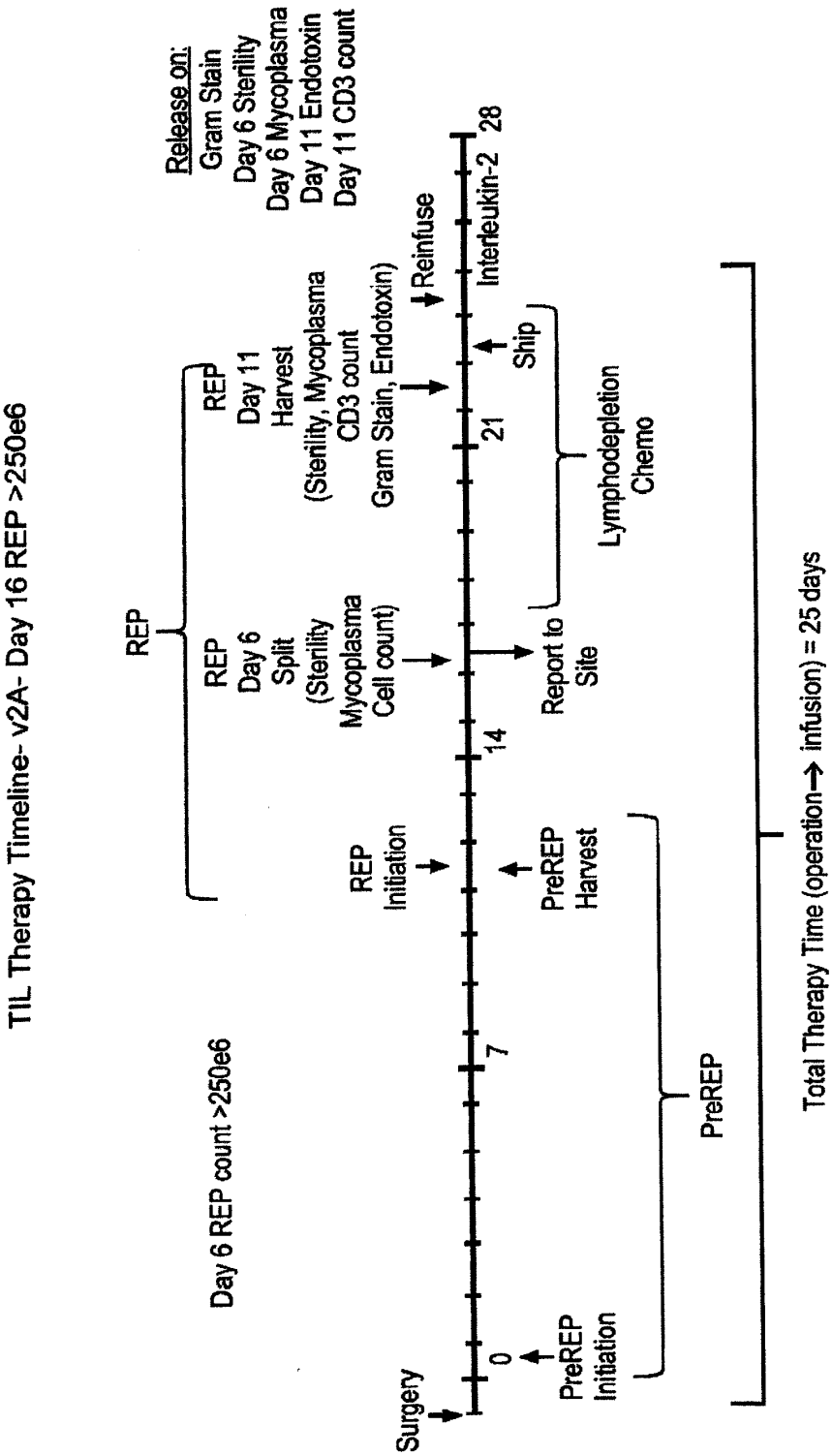

TIL Therapy Timeline- v2A- Day 16 REP >250e6
Release on:
Gram Stain
Day 6 Sterility
Day 6 Mycoplasma
Day 11 Endotoxin
Day 11 CD3 count
REP
REP
Day 6
Split
(Sterility
Mycoplasma
Cell count)
REP
Day 11
Harvest
(Sterility, Mycoplasma
CD3 count
Gram Stain, Endotoxin)
Reinfuse
Interleukin-2
Ship
Lymphodepletion
Chemo
Report to
Site
REP
Initiation
PreREP
Harvest
PreREP
Initiation
Surgery
Day 6 REP count >250e6
PreREP
Total Therapy Time (operation→ infusion) = 25 days
0
7
14
21
28

Figure 4

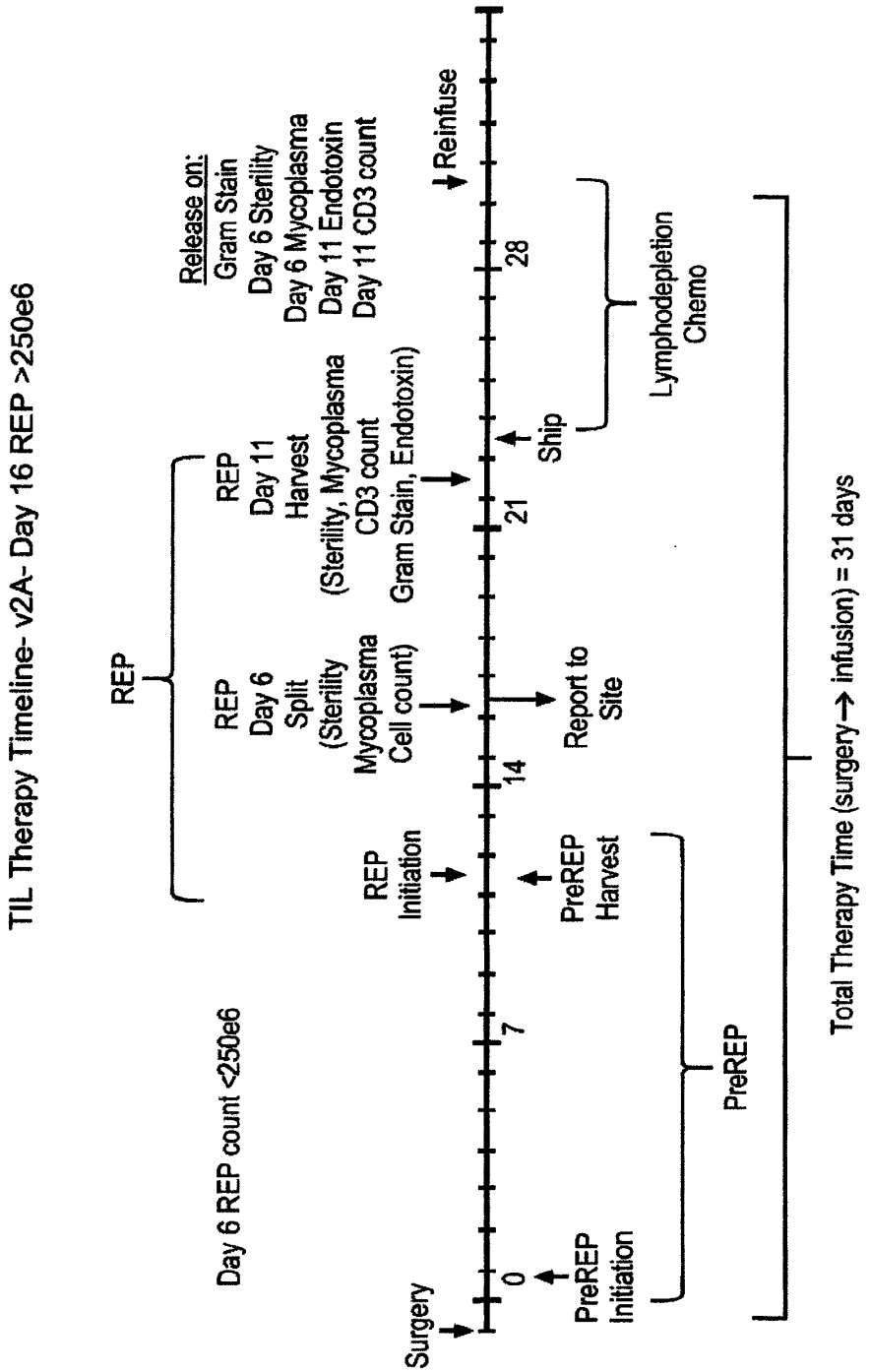

TIL Therapy Timeline- v2A- Day 16 REP >250e6
Day 6 REP count <250e6
REP
REP Initiation
REP Day 6 Split (Sterility Mycoplasma Cell count)
REP Day 11 Harvest (Sterility, Mycoplasma CD3 count Gram Stain, Endotoxin)
Release on:
Gram Stain
Day 6 Sterility
Day 6 Mycoplasma
Day 11 Endotoxin
Day 11 CD3 count
Reinfuse
Surgery
PreREP Initiation
PreREP Harvest
Report to Site
Ship
Lymphodepletion Chemo
PreREP
0
7
14
21
28
Total Therapy Time (surgery→ infusion) = 31 days

Figure 5

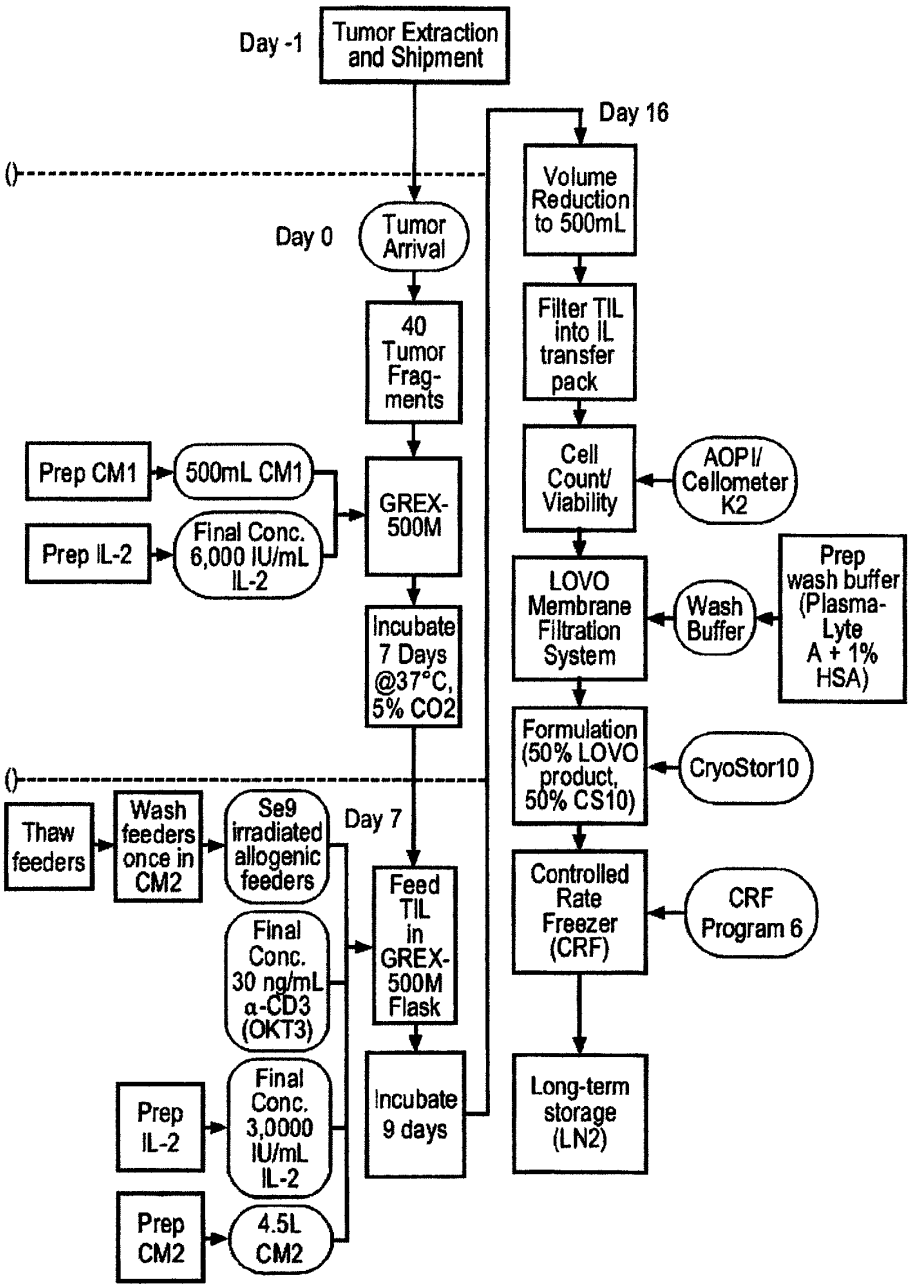

Day -1
Tumor Extraction and Shipment
Day 0
Tumor Arrival
40 Tumor Frag-ments
Prep CM1
500mL CM1
Prep IL-2
Final Conc. 6,000 IU/mL IL-2
GREX-500M
Incubate 7 Days @37°C, 5% CO2
Day 7
Thaw feeders
Wash feeders once in CM2
Se9 irradiated allogenic feeders
Final Conc. 30 ng/mL α-CD3 (OKT3)
Feed TIL in GREX-500M Flask
Prep IL-2
Final Conc. 3,0000 IU/mL IL-2
Incubate 9 days
Prep CM2
4.5L CM2
Day 16
Volume Reduction to 500mL
Filter TIL into IL transfer pack
Cell Count/ Viability
AOPI/ Cellometer K2
LOVO Membrane Filtration System
Wash Buffer
Prep wash buffer (Plasma-Lyte A + 1% HSA)
Formulation (50% LOVO product, 50% CS10)
CryoStor10
Controlled Rate Freezer (CRF)
CRF Program 6
Long-term storage (LN2)

Figure 6

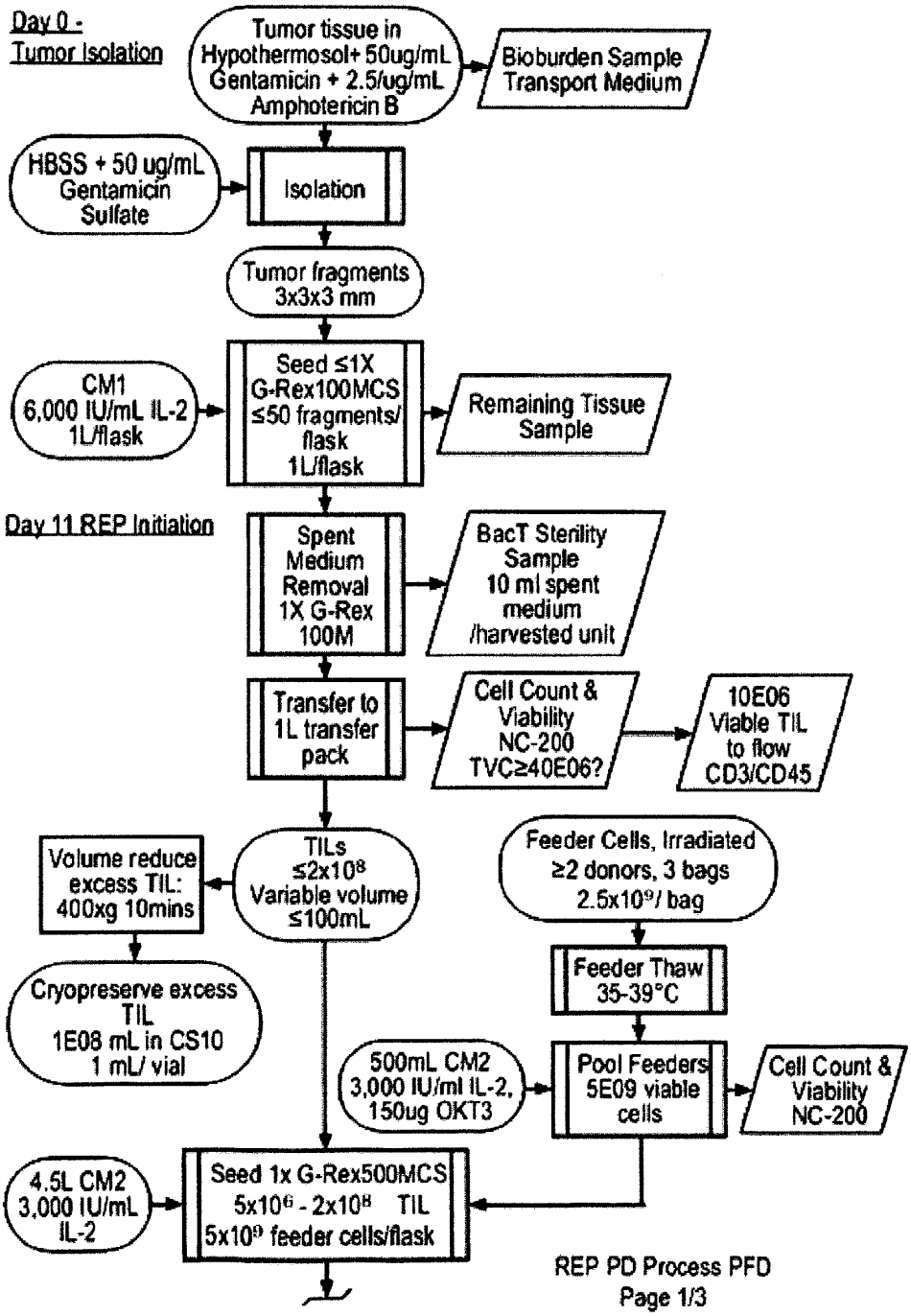


Figure 7b

Figure 7a

Figure 7a

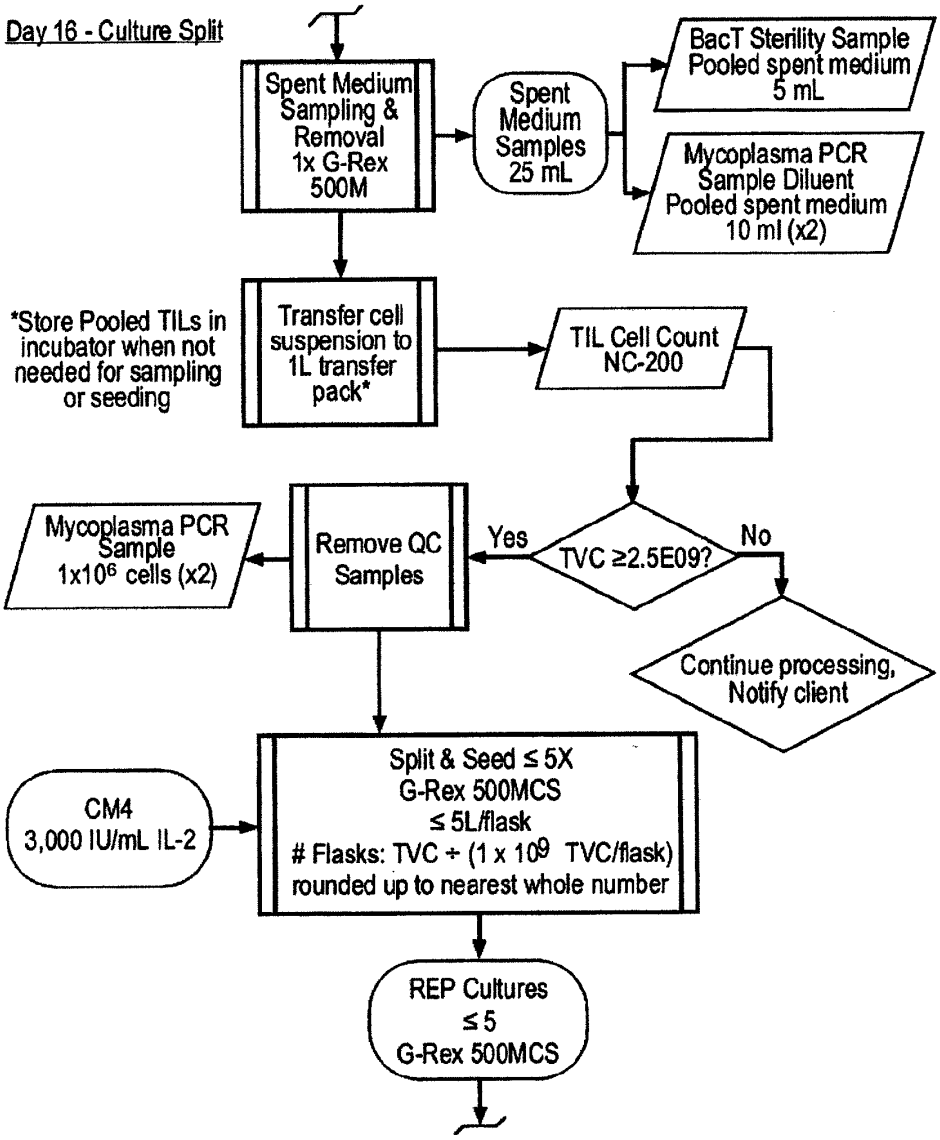


Figure 7c

REP PD Process PFD
Page 2/3

Figure 7b

Figure 7b

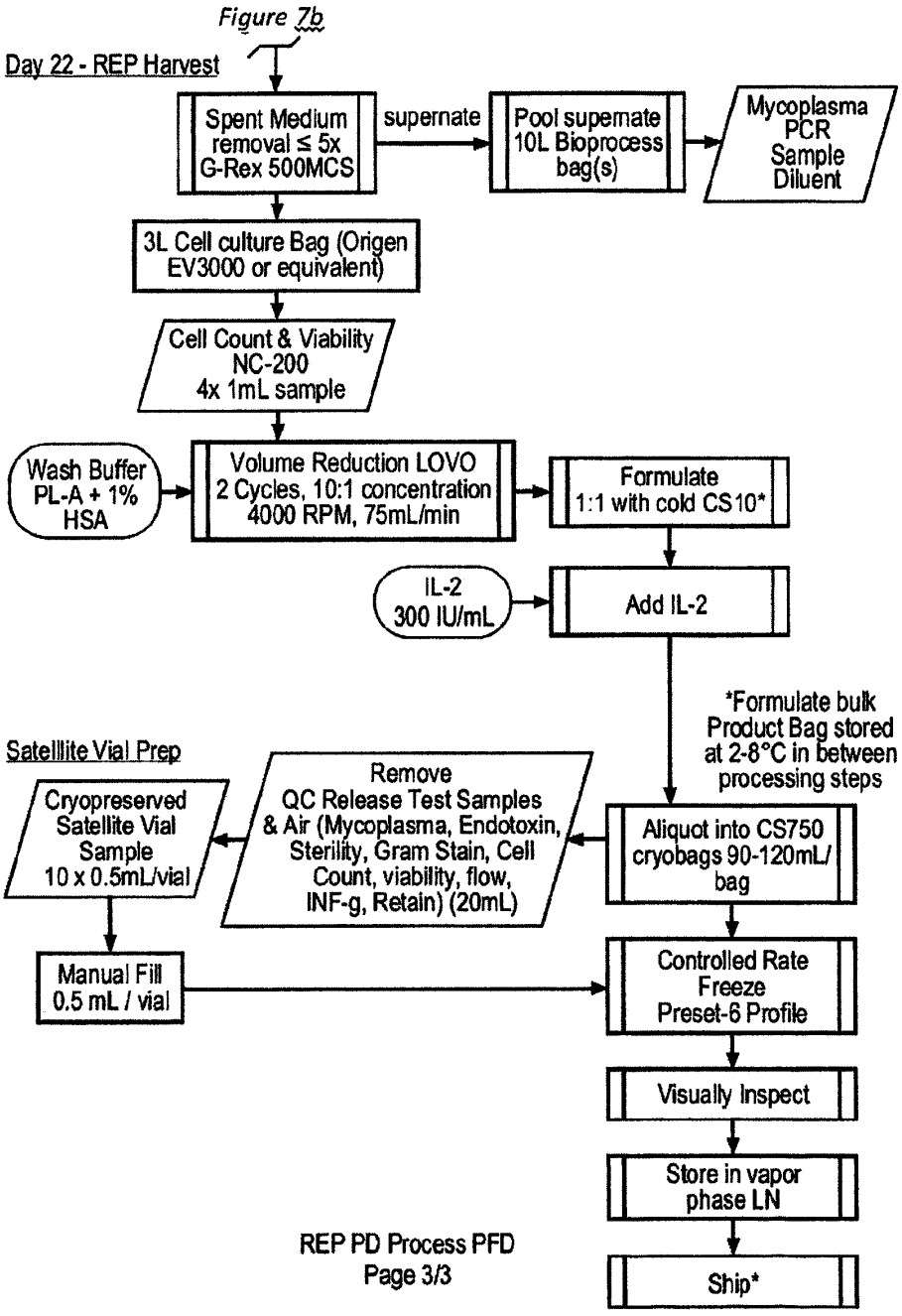


Figure 7c

Figure 8

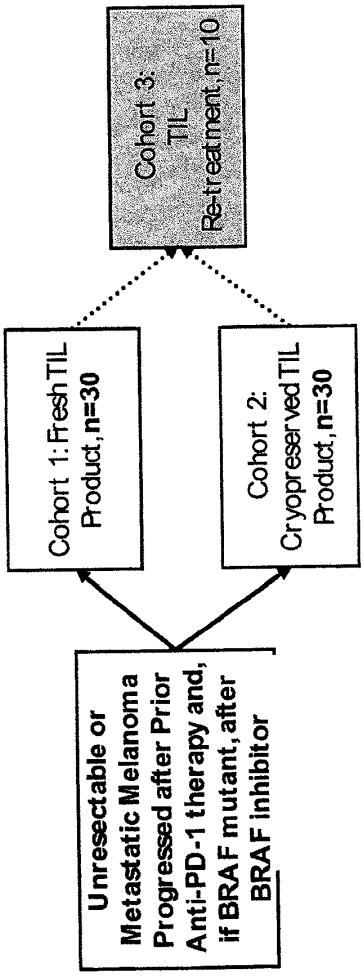

Unresectable or Metastatic Melanoma Progressed after Prior Anti-PD-1 therapy and, if BRAF mutant, after BRAF inhibitor
Cohort 1: Fresh TIL Product, n=30
Cohort 2: Cryopreserved TIL Product, n=30
Cohort 3: TIL Re-treatment, n=10

Figure 9

Process 2A: about 22 days from Steps A - E

1. **STEP A**

Obtain Patient Tumor Sample

2. **STEP B**

Fragmentation and First Expansion

3 days to 14 days

3. **STEP C**

First Expansion to Second Expansion Transition

No Storage and Closed System

4. **STEP D**

Second Expansion

IL-2, OKT-3, and antigen-presenting feeder cells

Closed System

5. **STEP E**

Harvest TILS from Step D

Closed System

6. **STEP F**

Final Formulation and/or Transfer to Infusion Bag

(optionally cryopreserve)

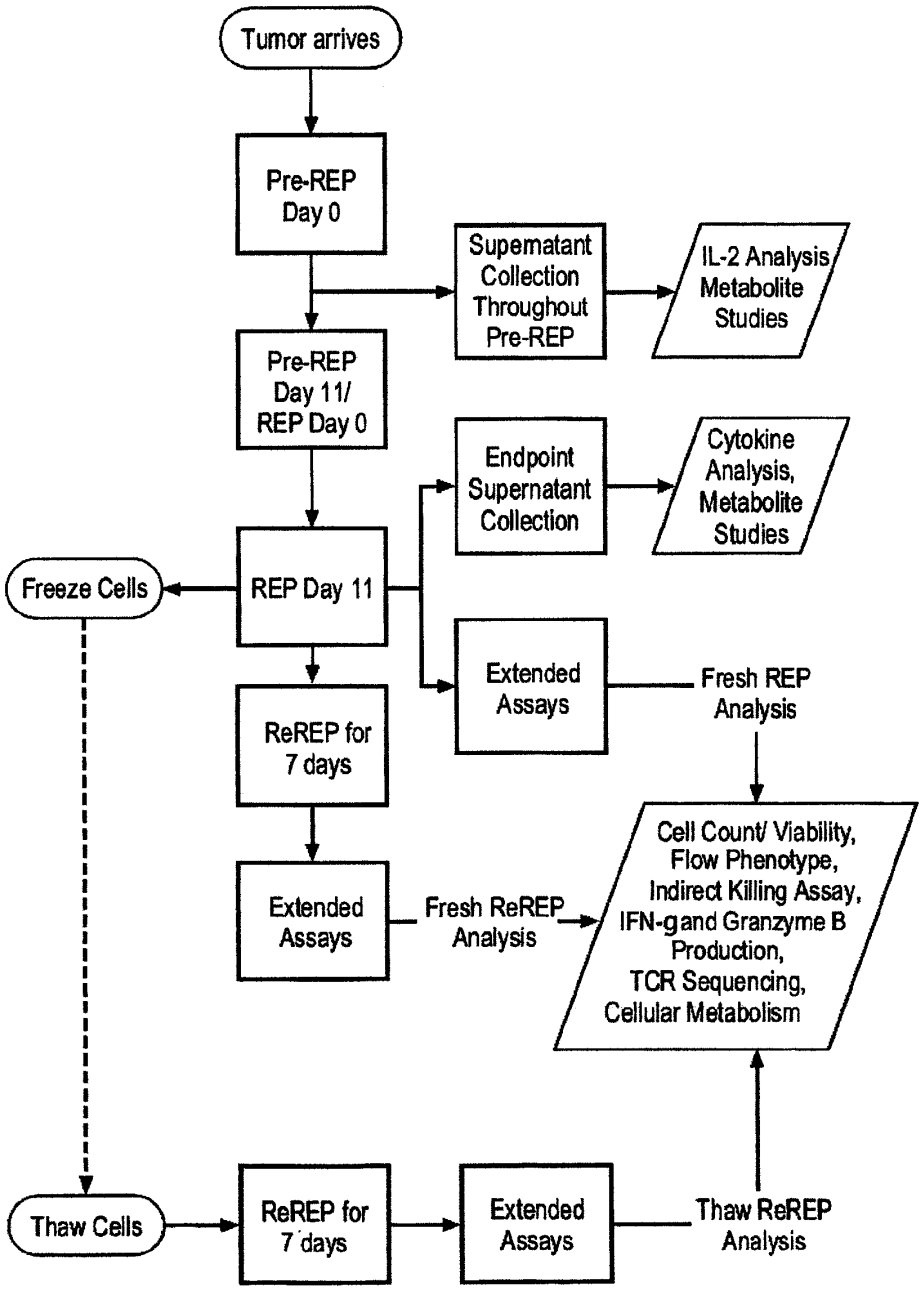

Tumor arrives
Pre-REP Day 0
Supernatant Collection Throughout Pre-REP
IL-2 Analysis Metabolite Studies
Pre-REP Day 11/ REP Day 0
Endpoint Supernatant Collection
Cytokine Analysis, Metabolite Studies
Freeze Cells
REP Day 11
Extended Assays
Fresh REP Analysis
ReREP for 7 days
Extended Assays
Fresh ReREP Analysis
Cell Count/ Viability, Flow Phenotype, Indirect Killing Assay, IFN-g and Granzyme B Production, TCR Sequencing, Cellular Metabolism
Thaw Cells
ReREP for 7 days
Extended Assays
Thaw ReREP Analysis

Figure 10

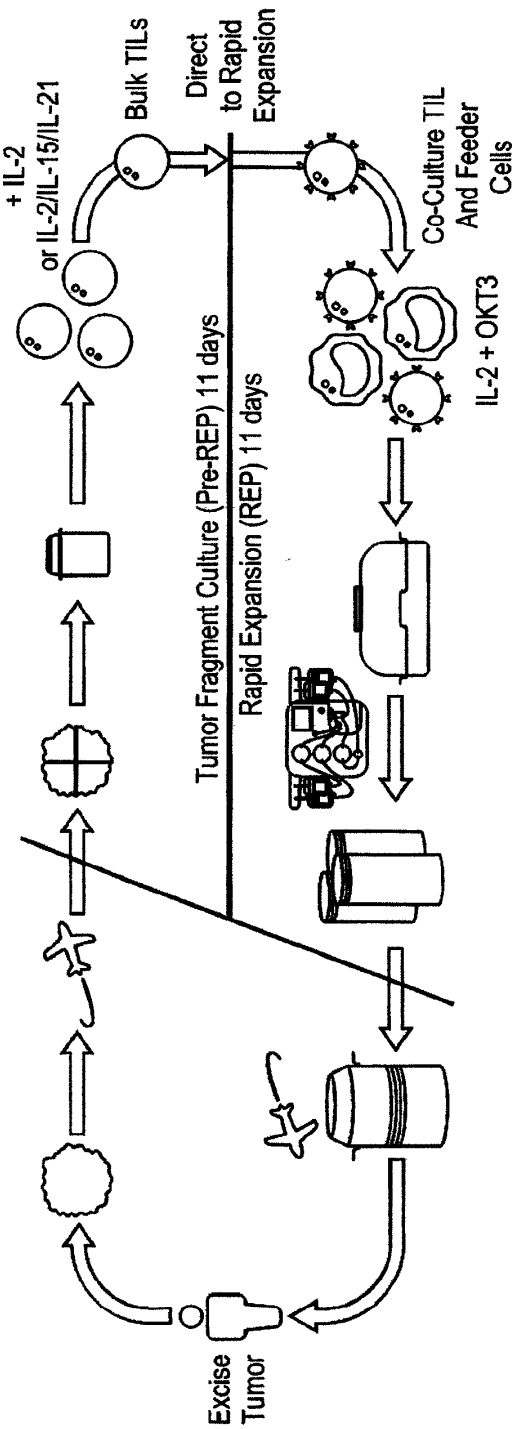

Excise Tumor
Tumor Fragment Culture (Pre-REP) 11 days
Rapid Expansion (REP) 11 days
+ IL-2 or IL-2/IL-15/IL-21
Bulk TILs
Direct to Rapid Expansion
Co-Culture TIL And Feeder Cells
IL-2 + OKT3

Figure 11

Figure 12

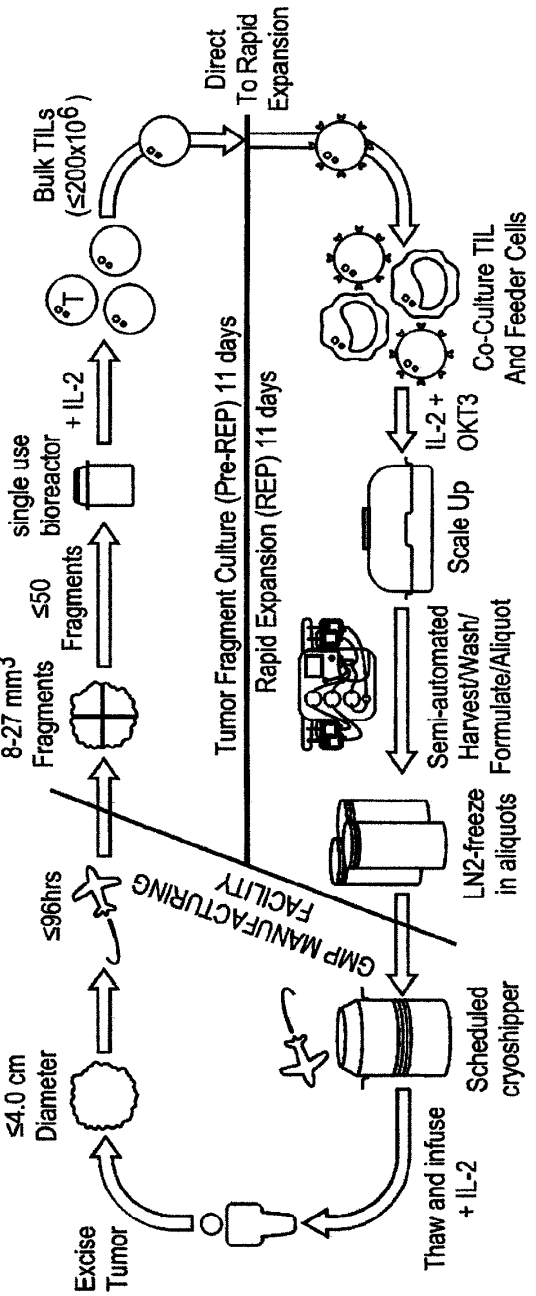

Excise Tumor
≤4.0 cm Diameter
≤96hrs
GMP MANUFACTURING FACILITY
8-27 mm3 Fragments
≤50 Fragments
Closed single use bioreactor
+ IL-2
Bulk TILs (≤200x10^6)
Tumor Fragment Culture (Pre-REP) 11 days
Rapid Expansion (REP) 11 days
Direct To Rapid Expansion
Co-Culture TIL And Feeder Cells
IL-2 + OKT3
Scale Up
Semi-automated Harvest/Wash/ Formulate/Aliquot
LN2-freeze in aliquots
Scheduled cryoshipper
Thaw and infuse + IL-2

Figure 13

Process 1C: 43-55 Days for Steps A - E	Process 2A: about 22 days from Steps A - E
1. **STEP A** Obtain Patient Tumor Sample	2. **STEP A** Obtain Patient Tumor Sample
3. **STEP B** Fragmentation and First Expansion 11 days to 21 days	3. **STEP B** Fragmentation and First Expansion 3 days to 14 days
3. **STEP C** First Expansion to Second Expansion Transition Optional Storage until Selection	4. **STEP C** First Expansion to Second Expansion Transition No Storage and Closed System
5. **STEP D** Second Expansion IL-2, OKT-3, antigen-presenting feeder cells Optionally repeat one or more times	5. **STEP D** Second Expansion IL-2, OKT-3, and antigen-presenting feeder cells Closed System
6. **STEP E** Harvest TILS from Step D	7. **STEP E** Harvest TILS from Step D Closed System
6. **STEP F** Final Formulation and/or Transfer to Infusion Bag	8. **STEP F** Final Formulation and/or Transfer to Infusion Bag (optionally cryopreserve)

Figure 14

Process Step	Process 1C Embodiment	Process 2A Embodiment	Advantages
Pre-REP	• 4 fragments per 10 GREX-10 flasks • 11-21 day duration	• 40 fragments per 1 GREX-100M flask • 11 day duration	• Increased tumor fragments per flask • Shortened culture time • Reduced number of steps • Amenable to closed system
Pre-REP to REP Transition	• Pre-REP TIL are frozen until phenotyped for selection then thawed to proceed to the REP (~day 30) • REP requires >40×10^6 TIL	• Pre-REP TIL directly move to REP on day 11 • REP requires 25-200×10^6 TIL	• Shortened pre-REP-to-REP process • Reduced number of steps • Eliminated phenotyping selection • Amenable to closed system
REP	• 6 GREX-100M flasks on REP day 0 • 5×10^6 TIL and 5×10^8 PBMC feeders per flask on REP day 0 • Split to 18-36 flasks on REP day 7 • 14 day duration	• 1 GREX-500M flask on day 11 • 25-200×10^6 TIL and $5\text{x}10^9$ PBMC feeders on day 11 • Split to ≤ 6 GREX-500M flasks on day 16 • 11 day duration	• Reduced number of steps • Shorter REP duration • Closed system transfer of TIL between flasks • Closed system media exchanges
Harvest	• TIL harvested via centrifugation	• TIL harvested via LOVO automated cell washing system'	• Reduced number of steps • Automated cell washing • Closed system • Reduced loss of product during wash
Final Formulation	• Fresh product in Hypothermosol • Single infusion bag • Limited shipping stability	• Cyropreserved product in PlasmaLyte-A + 1% HSA and CS10 stored in LN_2 • Multiple aliquots • Longer shipping stability	• Shipping flexibility • Flexible patient scheduling • More timely release testing
Overall Estimated Process Time	• 43-55 days	• 22 days	• Faster turnaround to patient

Figure 15

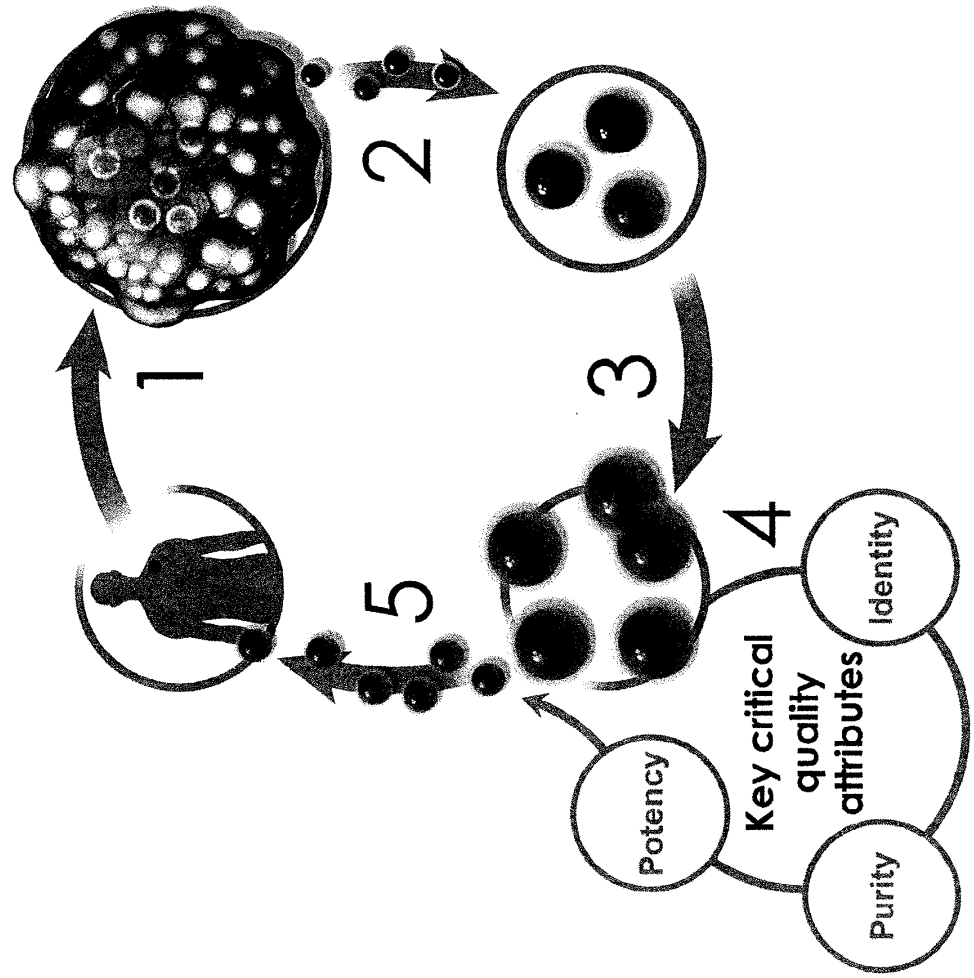

1
2
3
4
5
Key critical quality attributes
Potency
Identity
Purity

Figure 16

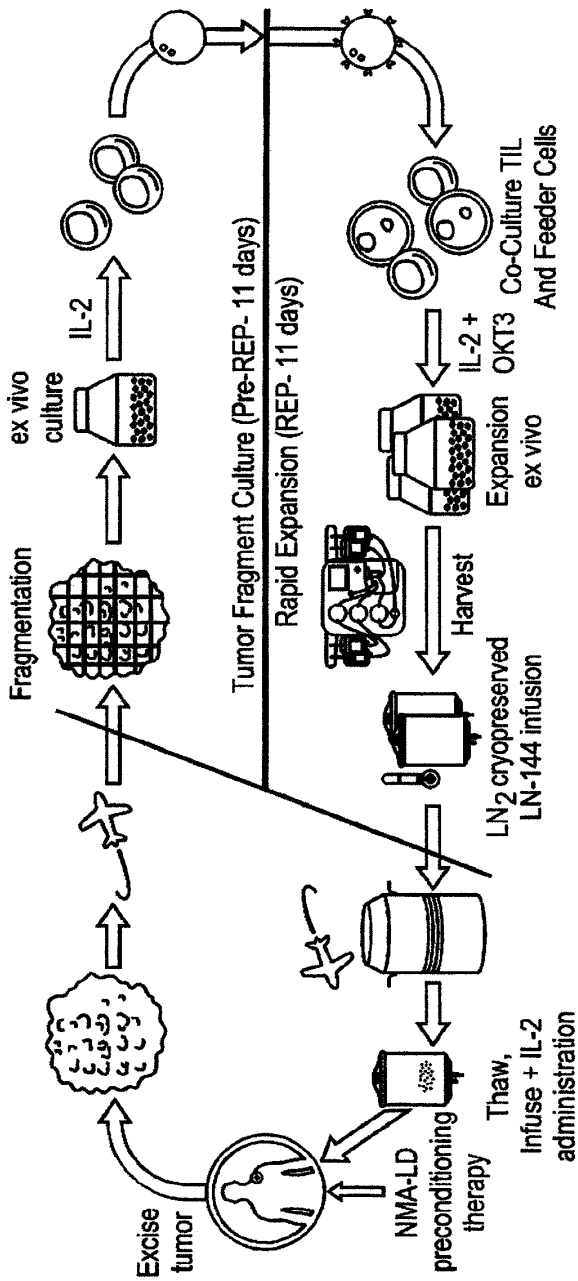
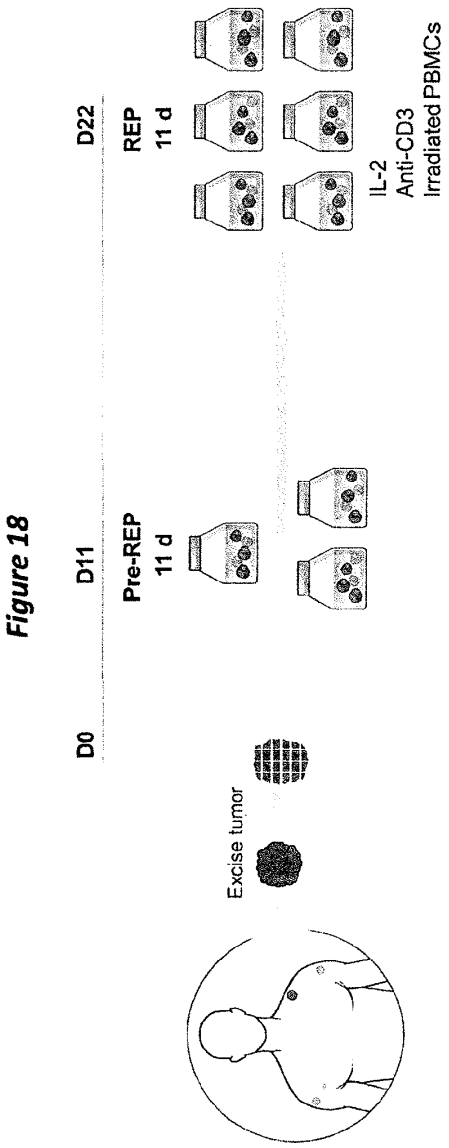

Excise tumor
NMA-LD preconditioning therapy
Thaw, Infuse + IL-2 administration
LN_2 cryopreserved LN-144 infusion
Harvest
IL-2 + OKT3
Expansion ex vivo
Co-Culture TIL And Feeder Cells
Fragmentation
ex vivo culture
IL-2
Tumor Fragment Culture (Pre-REP- 11 days)
Rapid Expansion (REP- 11 days)

Figure 17

PROCESS STEP	GEN 1	GEN 2	IMPACT
Fragment Culture	≤21 days, multiple bioreactors, multiple operator interventions	≤11 days, single closed bioreactor, no intervention	Shortens culture, reduces interventions
TIL selection	IL-2 expanded TIL cryopreserved, tested, selection based on phenotype, thaw, rest, co-culture	Bulk TIL direct to co-culture	Reduces steps, eliminates testing, increases clonal diversity
Harvest/ Wash	Manual volume reduction and harvest. Manual wash and concentration	Closed semi-automated volume reduction and harvest. Automated wash and concentration	Reduces operator interventions, reduces processing time, maintains functionally closed system
Formulation	Fresh hypothermic product (2-8°C)	Cryopreserved product (≤ -150°C)	Allows for global trials through increased flexibility in shipping and patient scheduling
Manufacturing Time	38 day process time	22 day process time	Turnaround to patient, clean room throughput, lower cost of goods

Figure 18


D0
D11
D22
Excise tumor
Pre-REP
11 d
REP
11 d
IL-2
Anti-CD3
Irradiated PBMCs

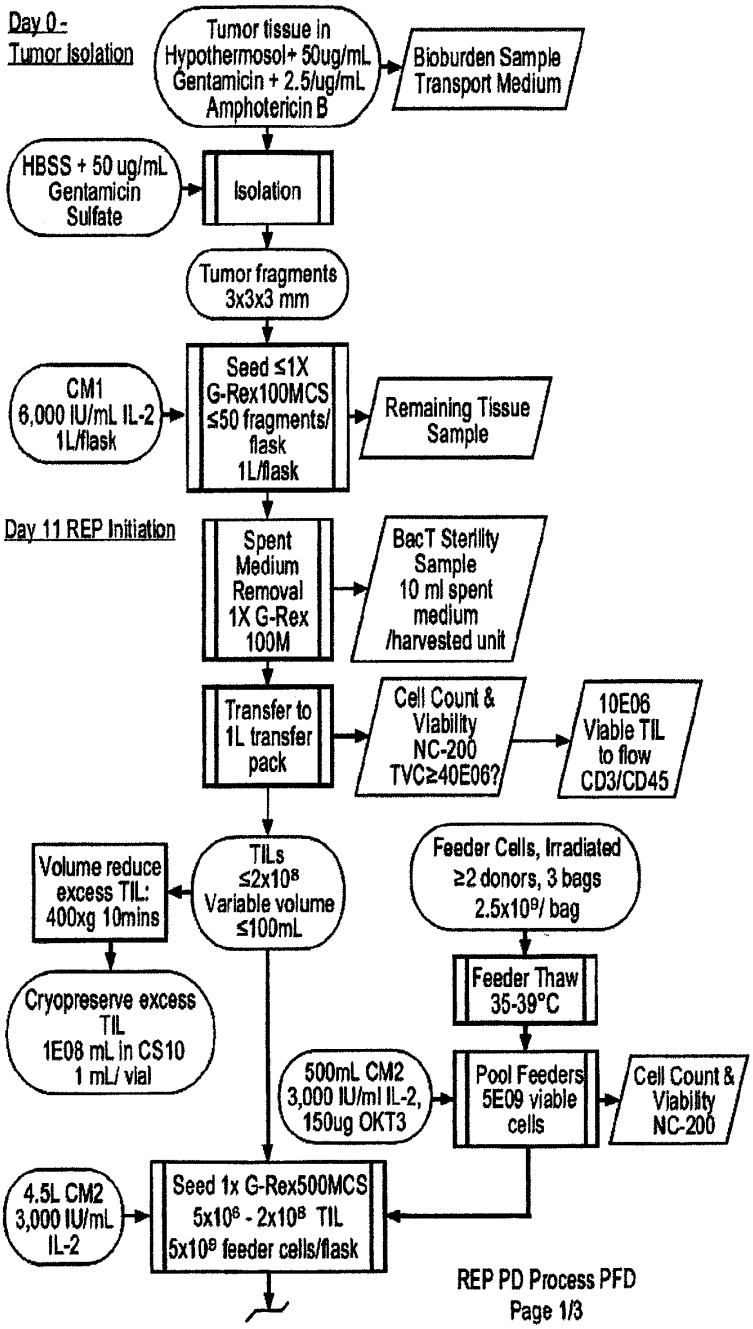

Day 0 -
Tumor Isolation
Tumor tissue in Hypothermosol+ 50ug/mL Gentamicin + 2.5/ug/mL Amphotericin B
Bioburden Sample Transport Medium
HBSS + 50 ug/mL Gentamicin Sulfate
Isolation
Tumor fragments 3x3x3 mm
CM1 6,000 IU/mL IL-2 1L/flask
Seed ≤1X G-Rex100MCS ≤50 fragments/ flask 1L/flask
Remaining Tissue Sample
Day 11 REP Initiation
Spent Medium Removal 1X G-Rex 100M
BacT Sterility Sample 10 ml spent medium /harvested unit
Transfer to 1L transfer pack
Cell Count & Viability NC-200 TVC≥40E06?
10E06 Viable TIL to flow CD3/CD45
Volume reduce excess TIL: 400xg 10mins
TILs ≤2x10⁸ Variable volume ≤100mL
Feeder Cells, Irradiated ≥2 donors, 3 bags 2.5x10⁹/ bag
Cryopreserve excess TIL 1E08 mL in CS10 1 mL/ vial
Feeder Thaw 35-39°C
500mL CM2 3,000 IU/ml IL-2, 150ug OKT3
Pool Feeders 5E09 viable cells
Cell Count & Viability NC-200
4.5L CM2 3,000 IU/mL IL-2
Seed 1x G-Rex500MCS 5x10⁶ - 2x10⁸ TIL 5x10⁹ feeder cells/flask
REP PD Process PFD
Page 1/3

Figure 19a

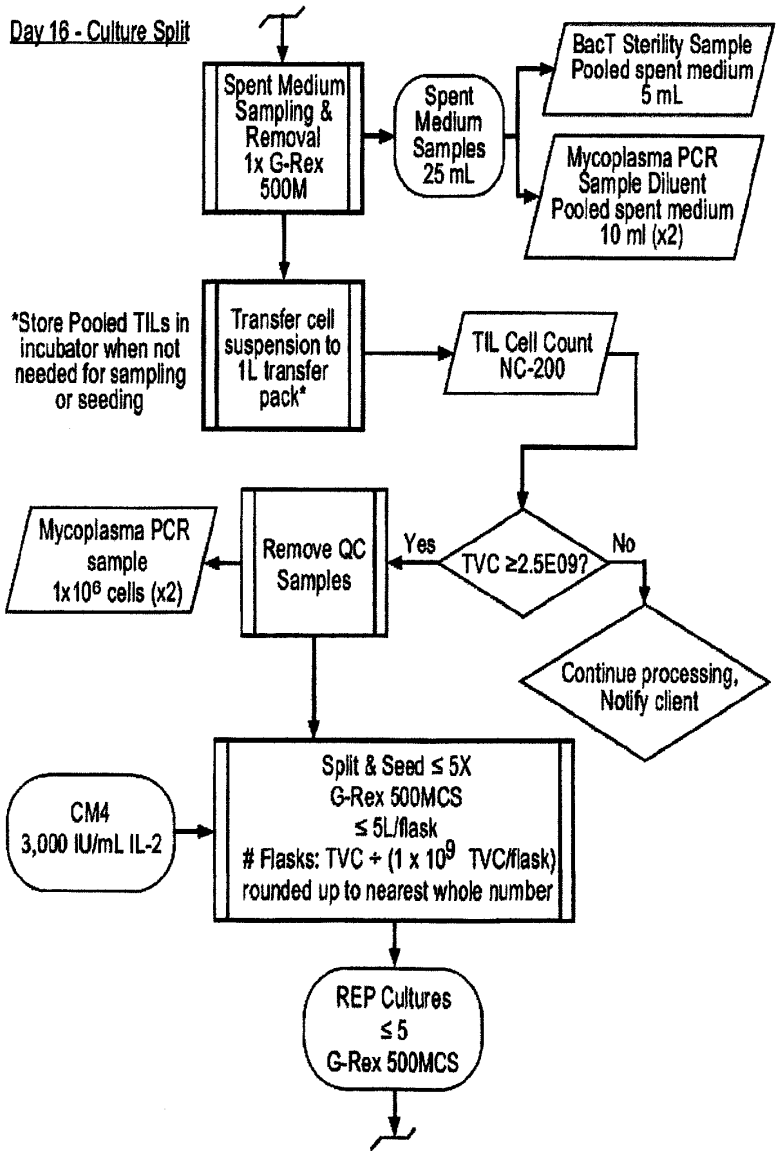

Day 16 - Culture Split
Spent Medium Sampling & Removal 1x G-Rex 500M
Spent Medium Samples 25 mL
BacT Sterility Sample Pooled spent medium 5 mL
Mycoplasma PCR Sample Diluent Pooled spent medium 10 ml (x2)
*Store Pooled TILs in incubator when not needed for sampling or seeding
Transfer cell suspension to 1L transfer pack*
TIL Cell Count NC-200
Mycoplasma PCR sample 1x10^6 cells (x2)
Remove QC Samples
Yes
TVC ≥2.5E09?
No
Continue processing, Notify client
CM4 3,000 IU/mL IL-2
Split & Seed ≤ 5X G-Rex 500MCS ≤ 5L/flask # Flasks: TVC ÷ (1 x 10^9 TVC/flask) rounded up to nearest whole number
REP Cultures ≤ 5 G-Rex 500MCS

Figure 19b

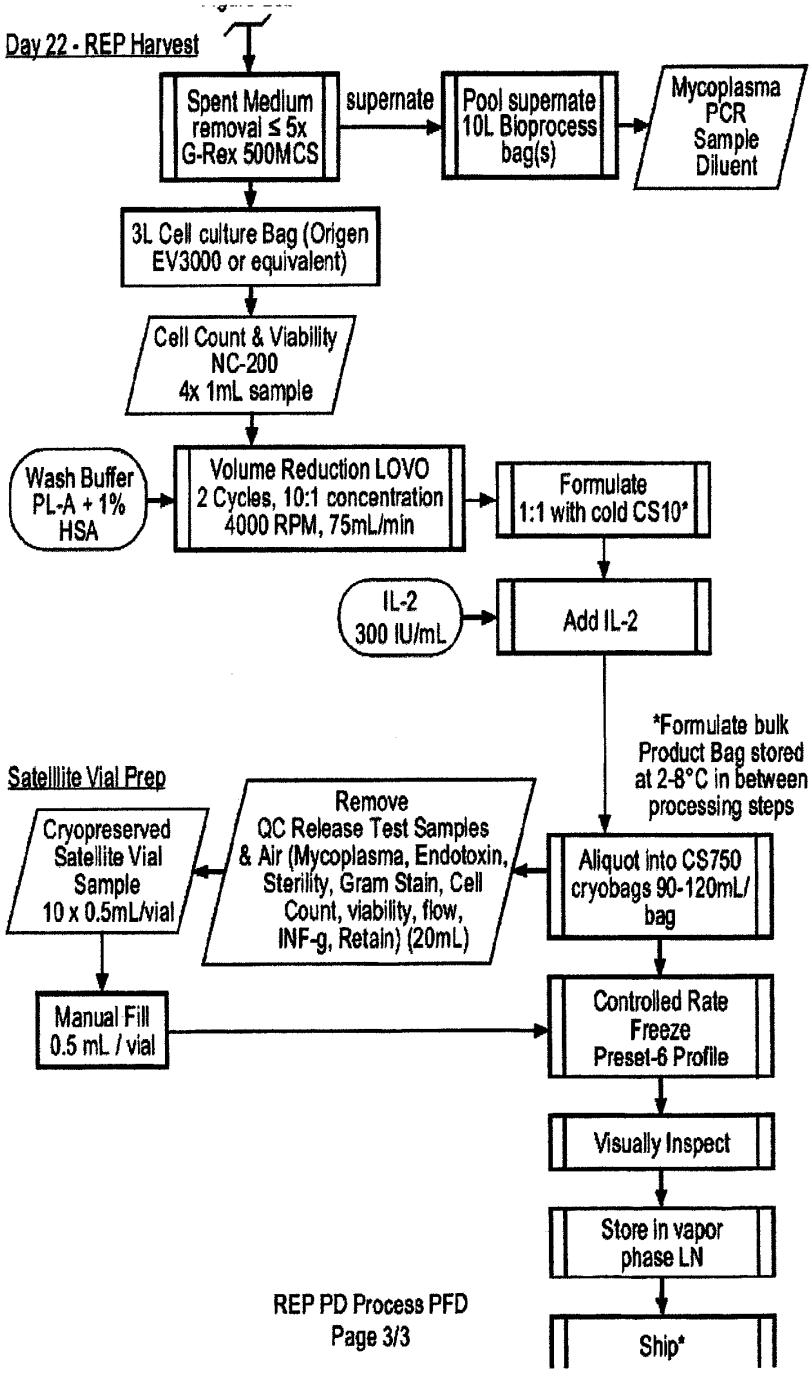

Day 22 - REP Harvest
Spent Medium removal ≤ 5x G-Rex 500MCS
supernate
Pool supernate 10L Bioprocess bag(s)
Mycoplasma PCR Sample Diluent
3L Cell culture Bag (Origen EV3000 or equivalent)
Cell Count & Viability NC-200 4x 1mL sample
Wash Buffer PL-A + 1% HSA
Volume Reduction LOVO 2 Cycles, 10:1 concentration 4000 RPM, 75mL/min
Formulate 1:1 with cold CS10*
IL-2 300 IU/mL
Add IL-2
*Formulate bulk Product Bag stored at 2-8°C in between processing steps
Satelllite Vial Prep
Cryopreserved Satellite Vial Sample 10 x 0.5mL/vial
Remove QC Release Test Samples & Air (Mycoplasma, Endotoxin, Sterility, Gram Stain, Cell Count, viability, flow, INF-g, Retain) (20mL)
Aliquot into CS750 cryobags 90-120mL/ bag
Manual Fill 0.5 mL / vial
Controlled Rate Freeze Preset-6 Profile
Visually Inspect
Store in vapor phase LN
Ship*
REP PD Process PFD
Page 3/3

Figure 19c

Figure 20

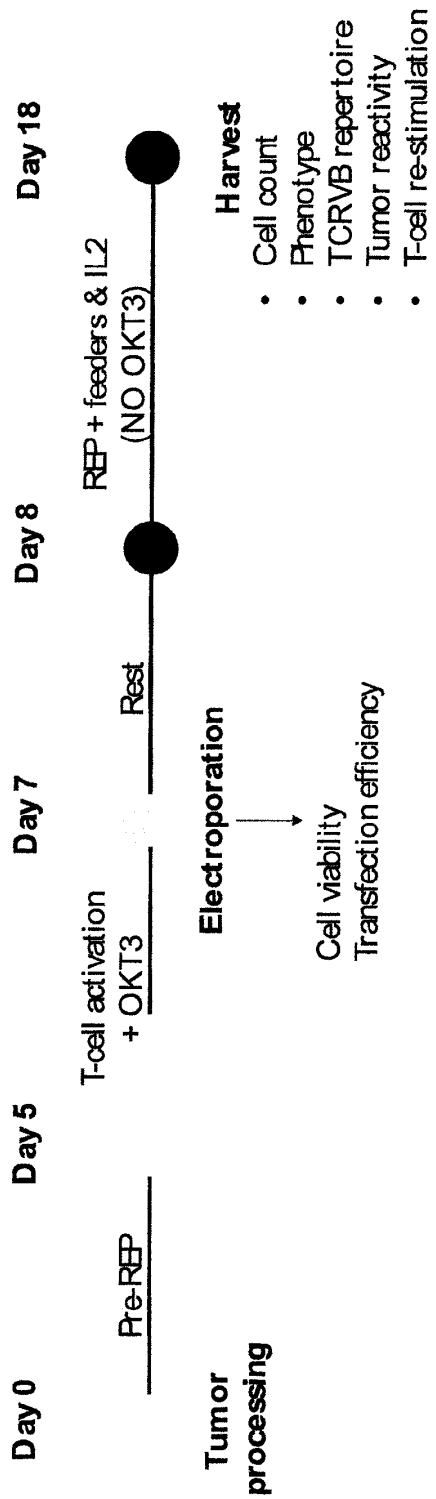
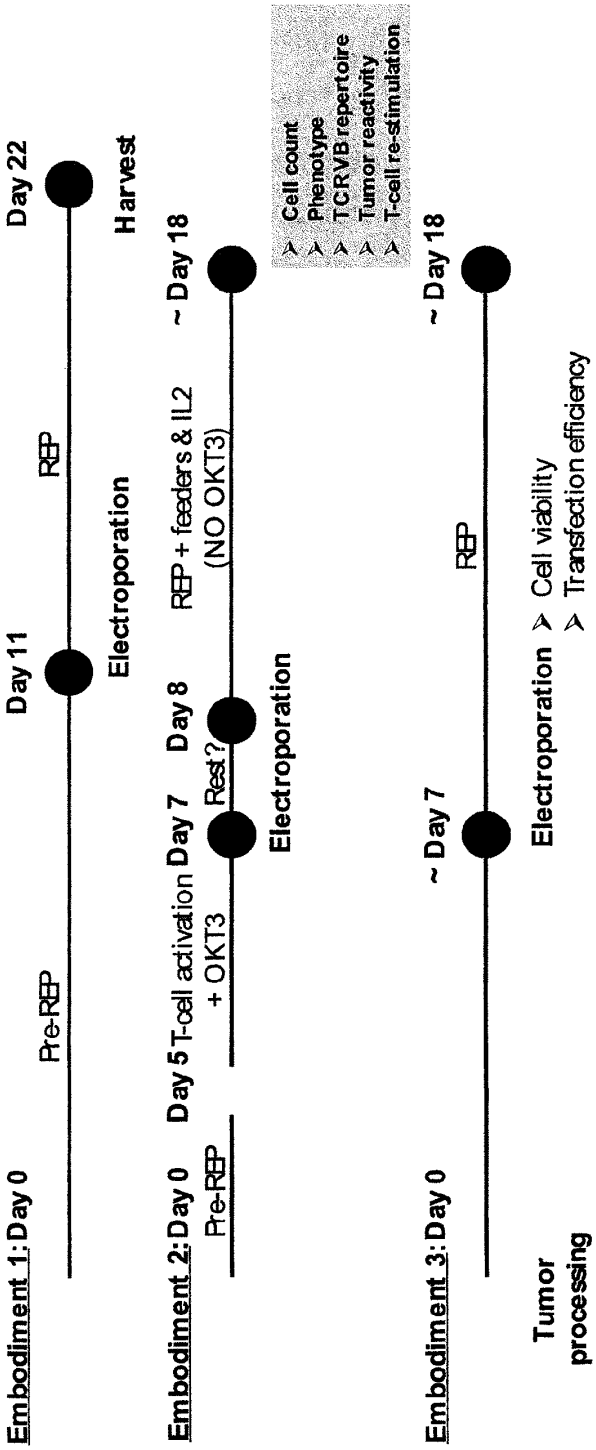

Day 0
Day 5
Day 7
Day 8
Day 18
Tumor processing
Pre-REP
T-cell activation + OKT3
Rest
REP + feeders & IL2 (NO OKT3)
Electroporation
Cell viability
Transfection efficiency
Harvest
Cell count
Phenotype
TCRVB repertoire
Tumor reactivity
T-cell re-stimulation

Figure 21


Embodiment 1: Day 0
Pre-REP
Day 11
REP
Day 22
Electroporation
Harvest
Embodiment 2: Day 0
Pre-REP
Day 5 T-cell activation + OKT3
Day 7
Rest?
Day 8
Electroporation
REP + feeders & IL2 (NO OKT3)
~ Day 18
Cell count
Phenotype
TCRVB repertoire
Tumor reactivity
T-cell re-stimulation
Embodiment 3: Day 0
Tumor processing
~ Day 7
Electroporation
REP
~ Day 18
Cell viability
Transfection efficiency

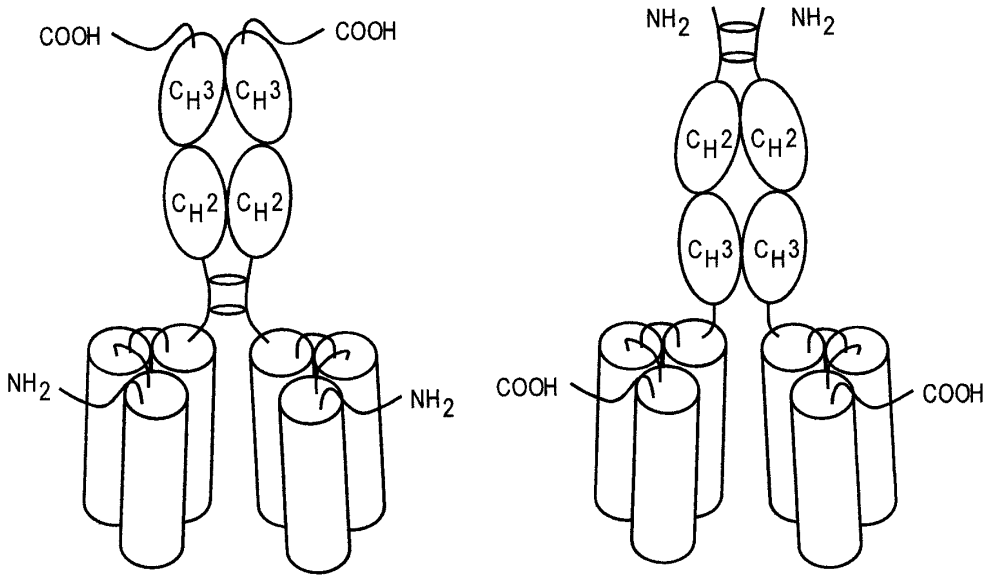


Figure 22

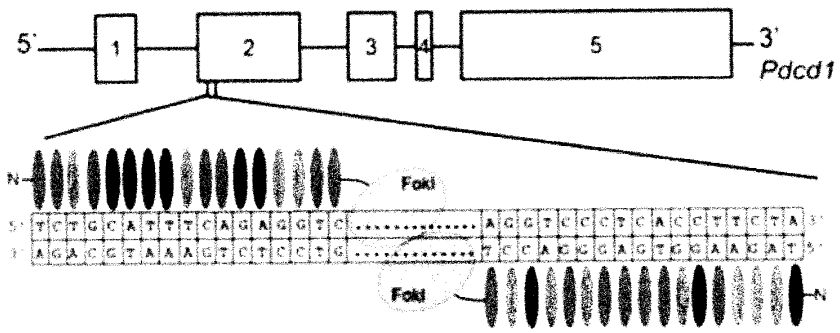


Figure 23