

Figure 1

Process 2A: about 22 days from initiation of First Expansion – Step E

1. STEP A

Obtain Patient Tumor Sample

2. STEP B

Fragmentation
Cryopreservation of Tumor Tissue Fragments
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)

Figure 2A

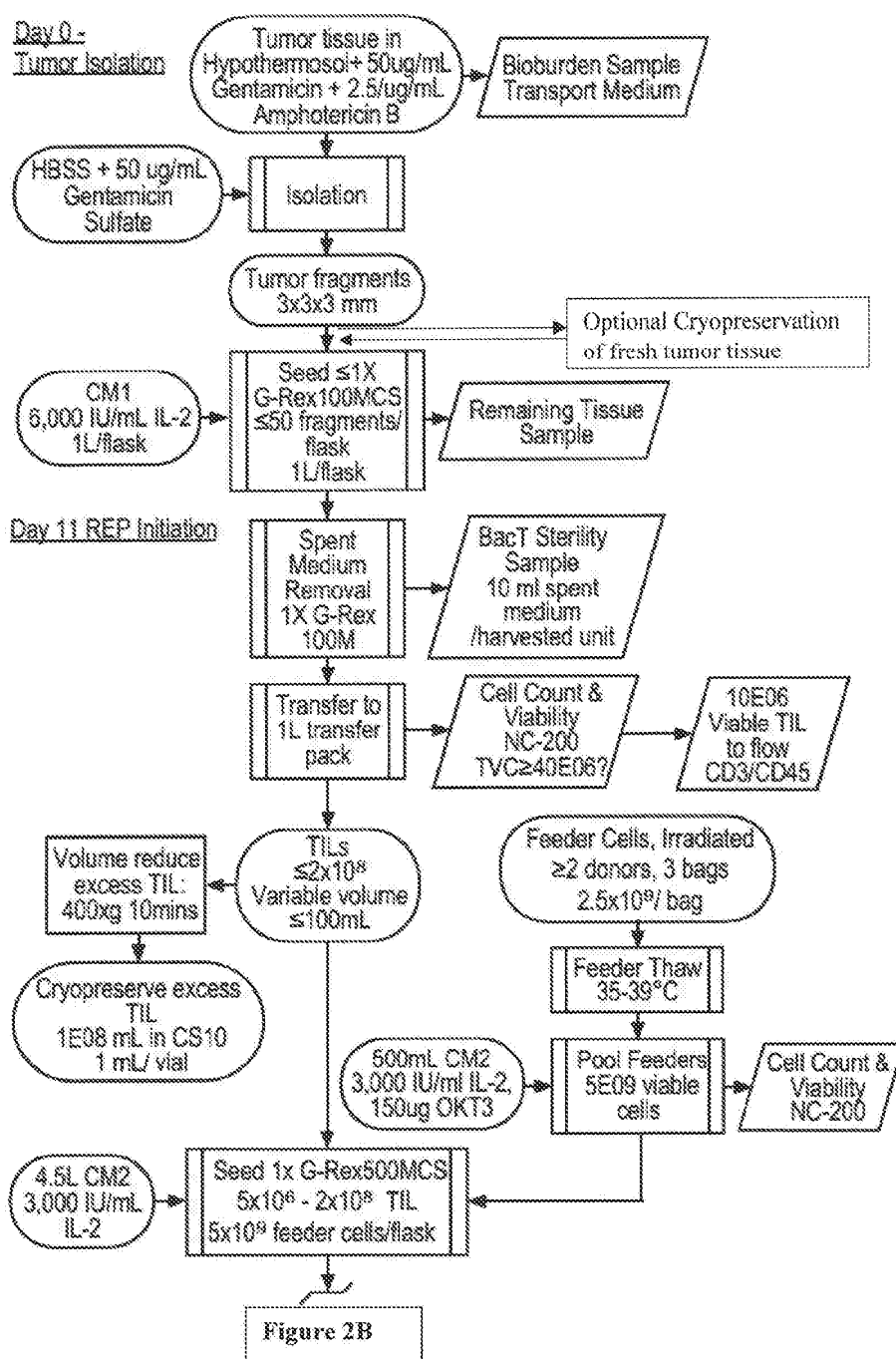


Figure 2B

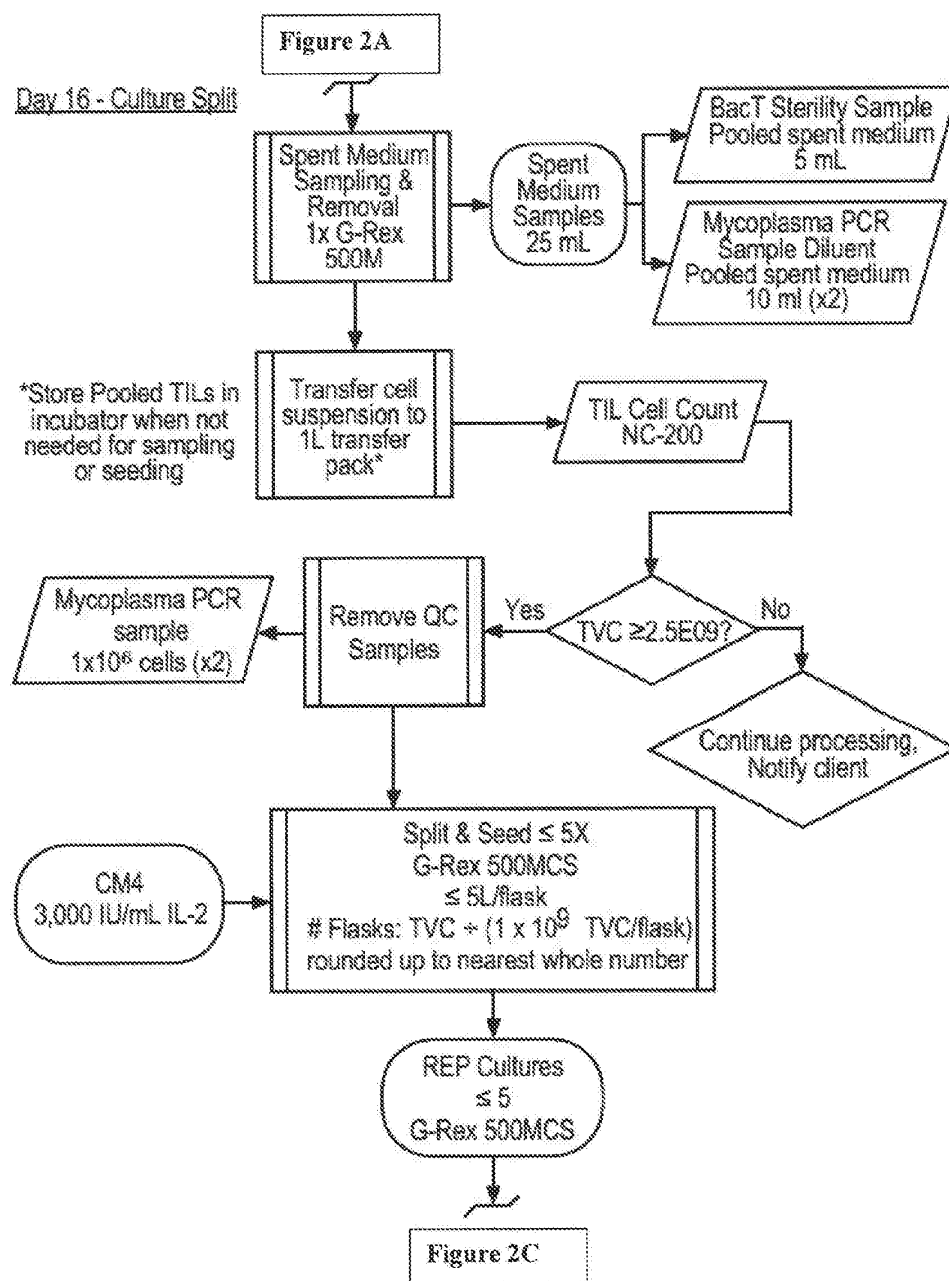
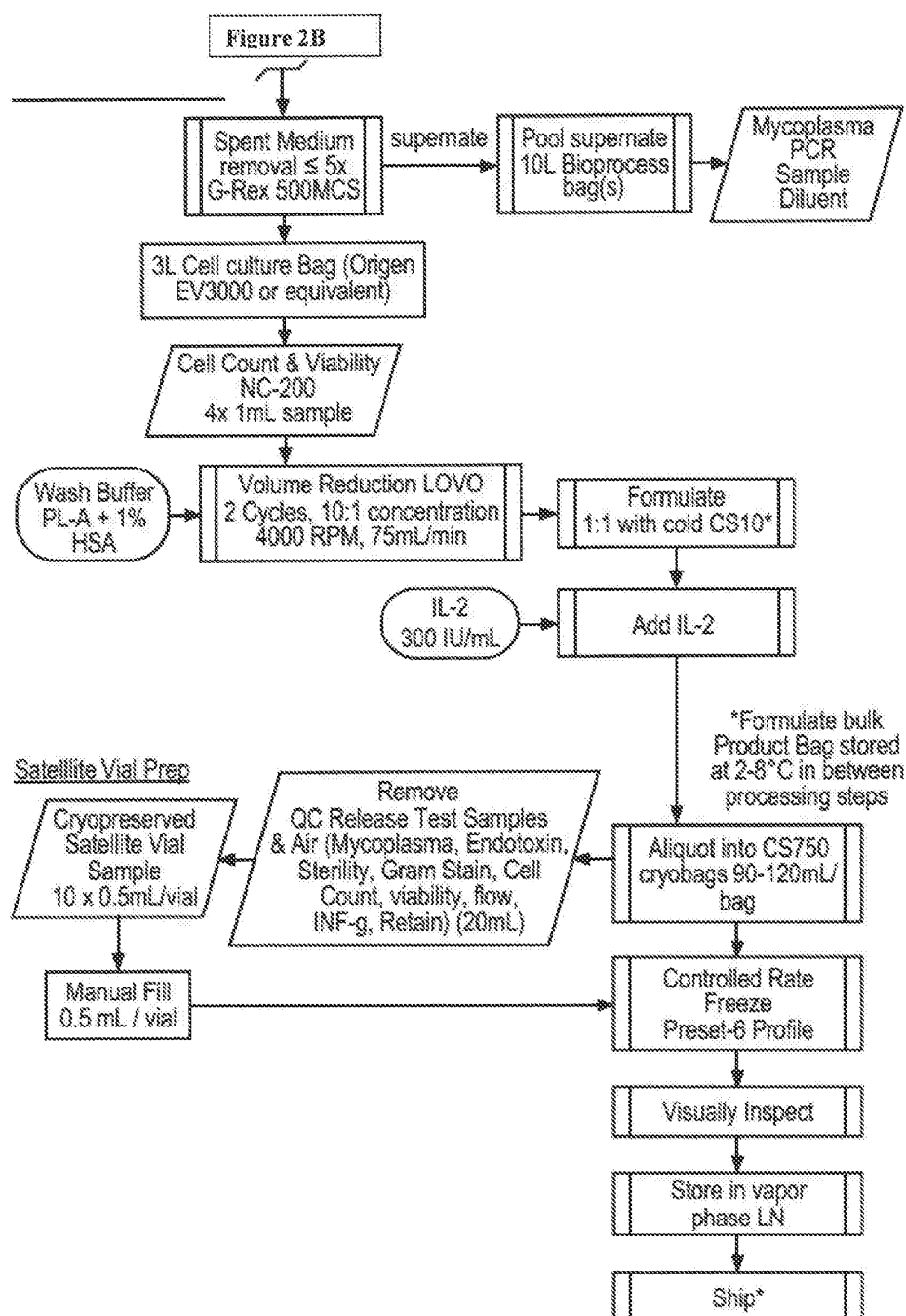


Figure 2C



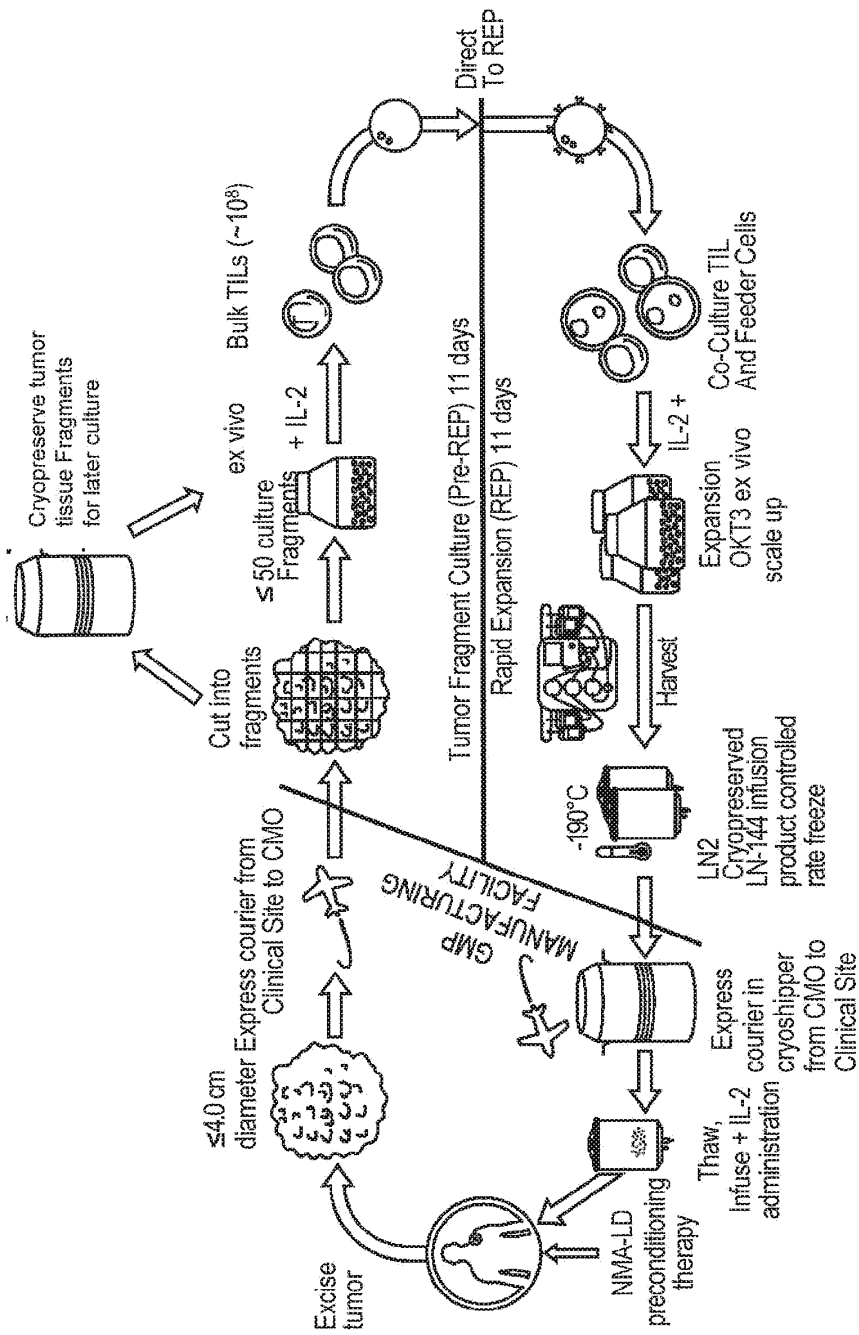


Figure 3

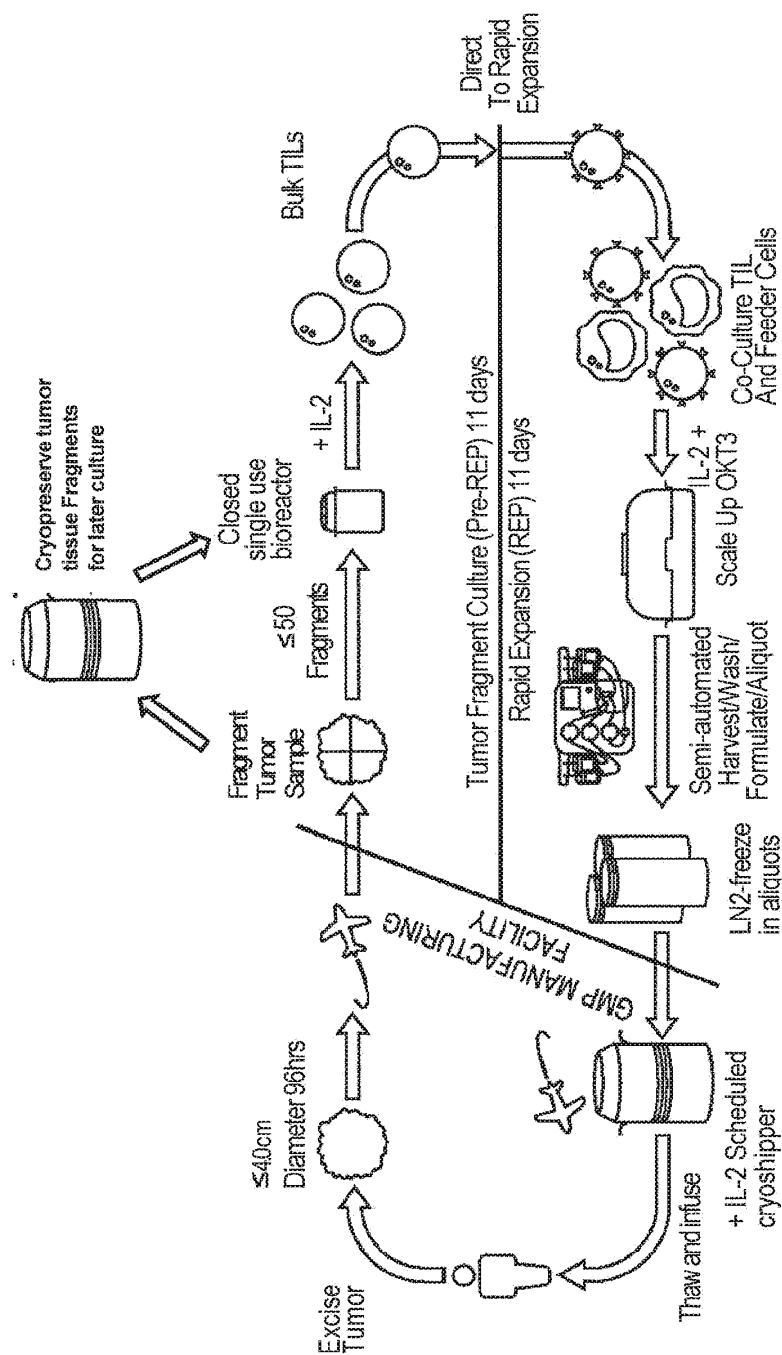


Figure 4

Figure 5

Process 1C 43 – 55 Days for Steps A - E	Process 2A About 22 Days from initiation of preREP to Step E
1. Step A Obtain Patient Tumor Sample	1. Step A Obtain Patient Tumor Sample
2. Step B Fragmentation and First Expansion 11 days to 21 days	2. Step B Fragmentation, optional cryopreservation of tumor fragments, and then First Expansion 11 days to 21 days (beginning from start of first expansion culture)
3. Step C First Expansion to Second Expansion Transition Optional Storage until Selection	3. Step C First Expansion to Second Expansion Transition No Storage and Closed System
4. Step D Second Expansion IL-2, OKT-3, antigen-presenting feeder cells Optionally repeat one or more times	4. Step D Second Expansion IL-2, OKT-3, antigen-presenting feeder cells Closed System
5. Step E Harvest TILs from Step D	5. Step E Harvest TILs from Step D Closed System
6. Step F Final Formulation and/or Transfer to Infusion Bag	6. Step F Final Formulation and/or Transfer to Infusion Bag Optional cryopreservation

Figure 6

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 $>40 \times 10^6$ TIL	- Pre-REP TIL directly move to REP on day 11 - REP requires 25-200 $\times 10^6$ 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 5×10^5 TIL and 5×10^4 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 $\times 10^6$ TIL and 5×10^5 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 LN₂ - 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

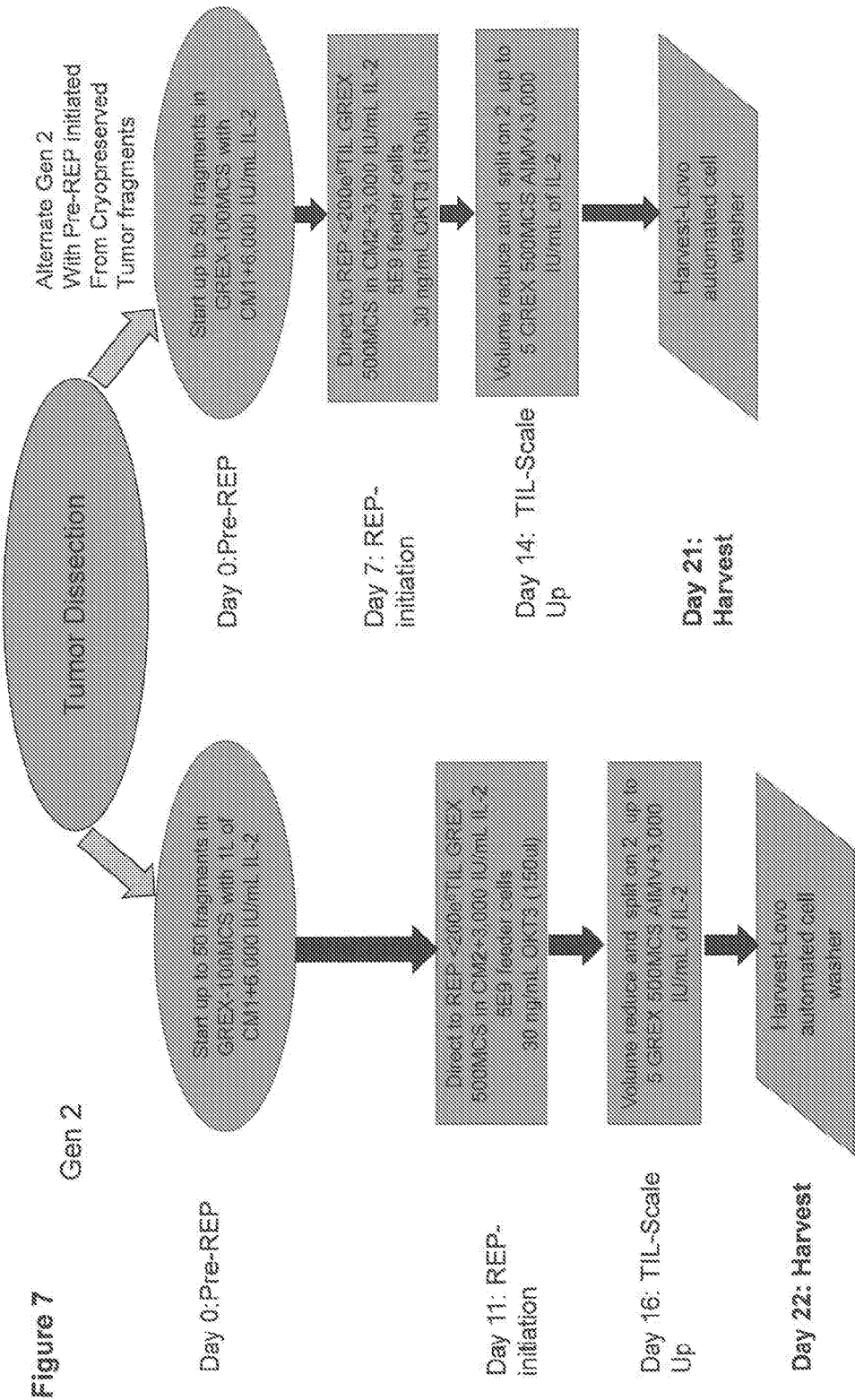


Figure 8

- Pre-REP TVC from Gen2 were 100e6 on Day 11
- Pre-REP TVC from Gen 2.2 were 0.8e6 on Day 7
- Pre-REP yield from Gen 2.2 were ~ 1% of Gen 2 control

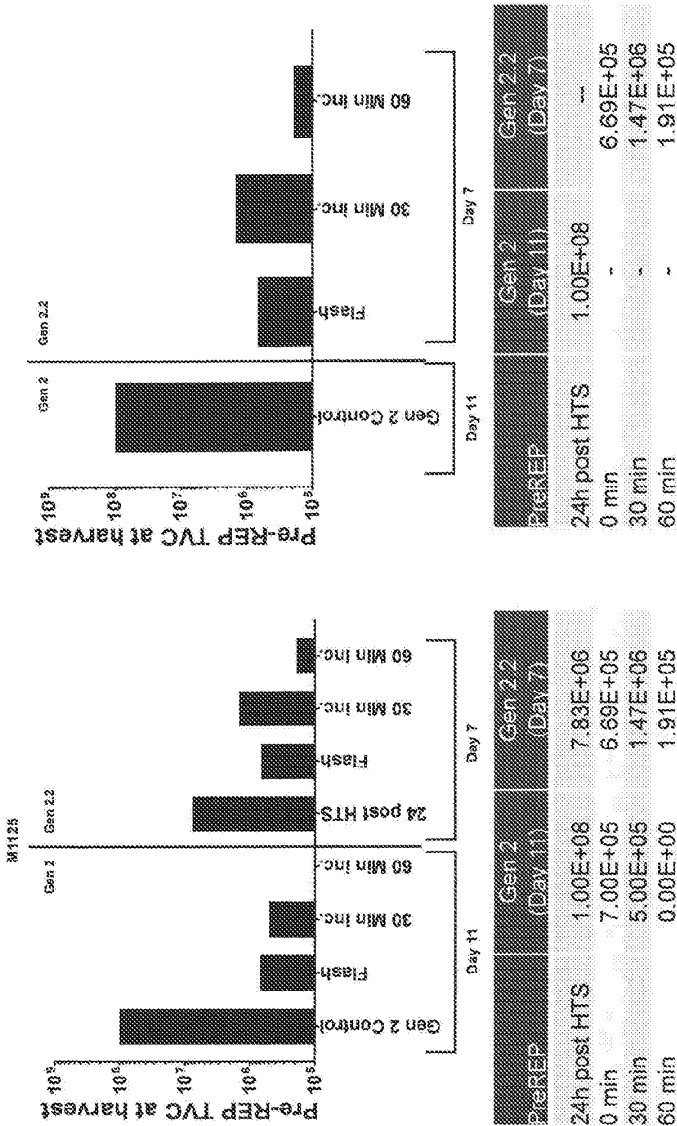


Figure 9

- Total REP TVC from Gen 2 were 2.5e9 on Day 22
- Total REP TVC from Gen 2.2 were 2.2, 2.2, e9 on Day 21
- Total REP yield from Gen 2.2 were ~ 86% of Gen 2

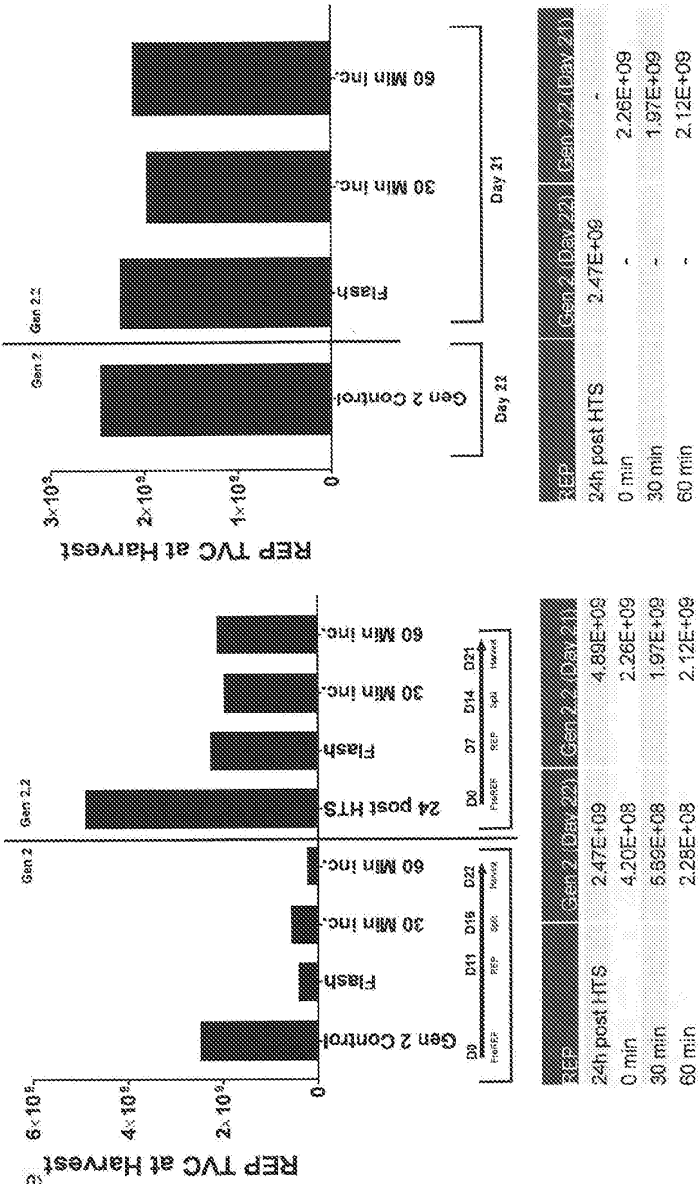


Figure 10

- REP TIL from Gen2 produced 6180 pg/mL IFN γ on Day 22
- REP TIL from Gen2.2 produced 10520, 12612, 11618 pg/mL IFN γ on Day 22

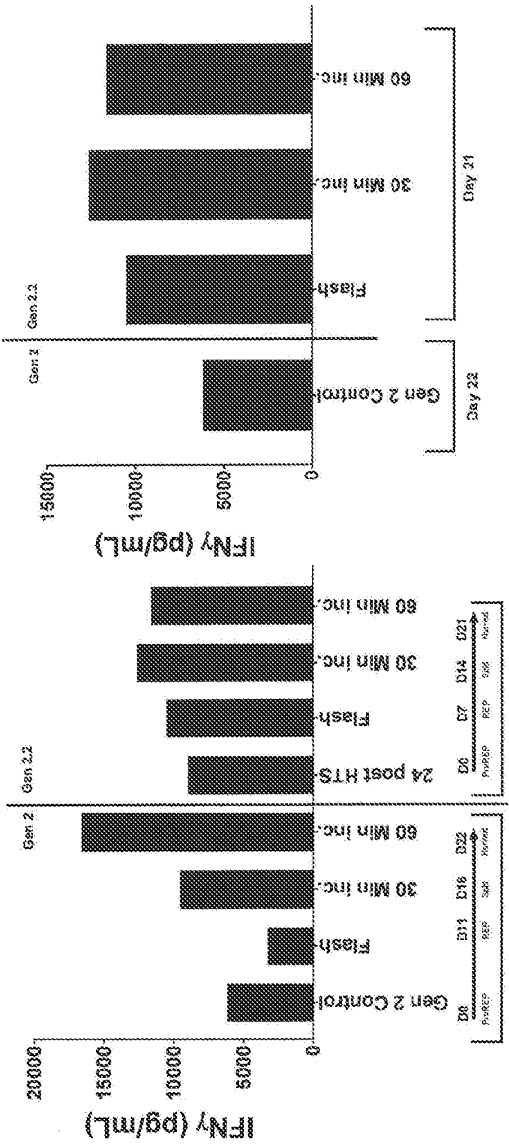
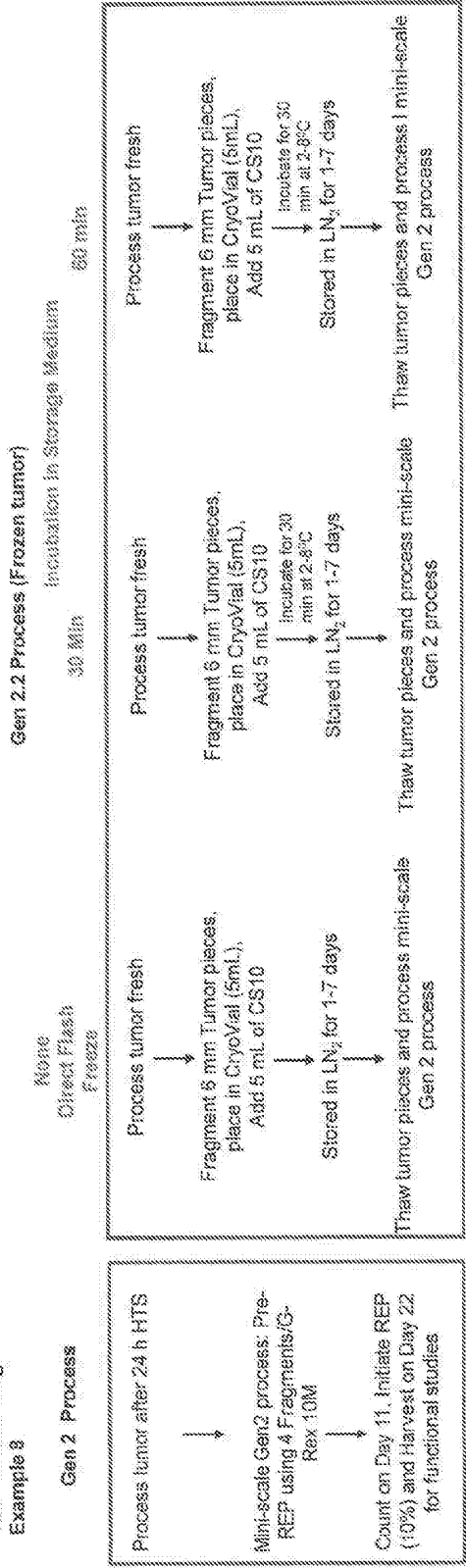


Figure 11
Tumor Processing
Example 8



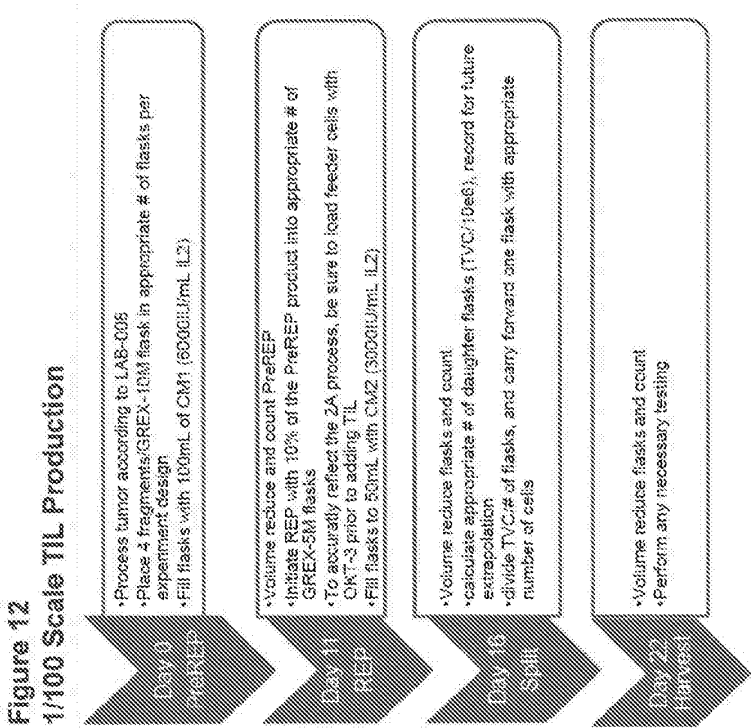


FIG. 13A

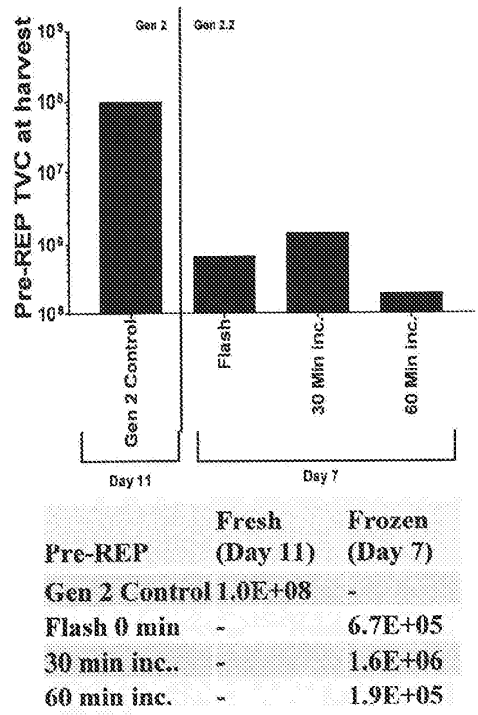


FIG. 13B

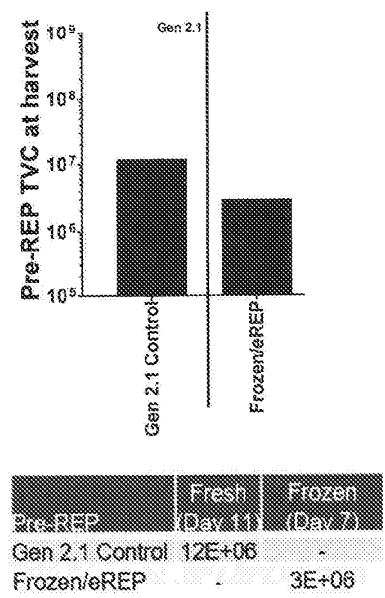


FIG. 13C

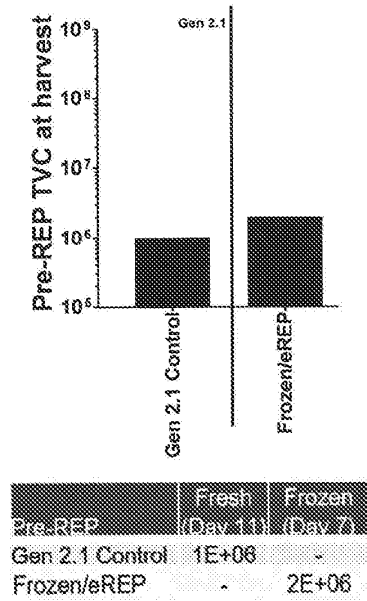


FIG. 13D

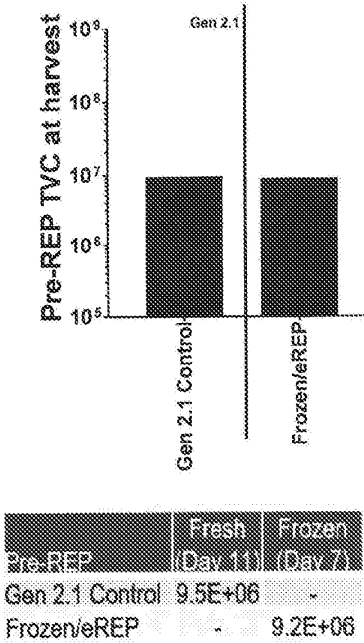


FIG. 13E

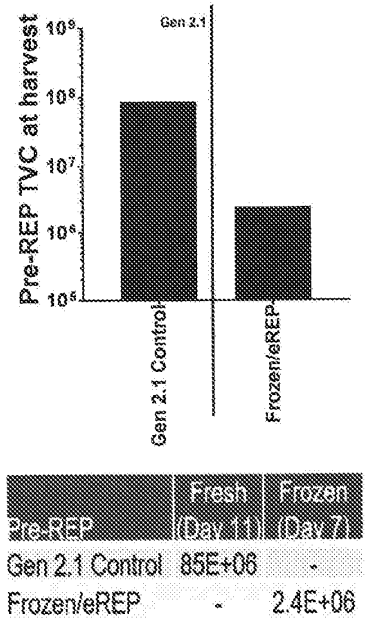
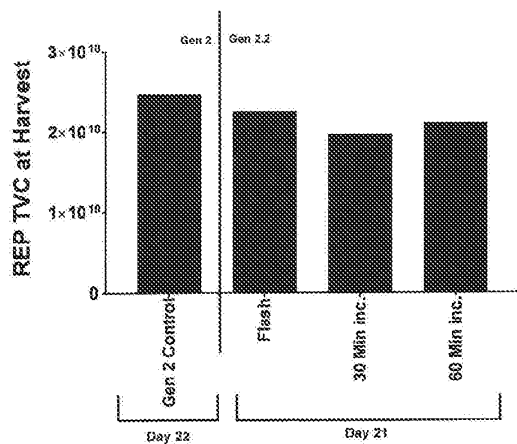
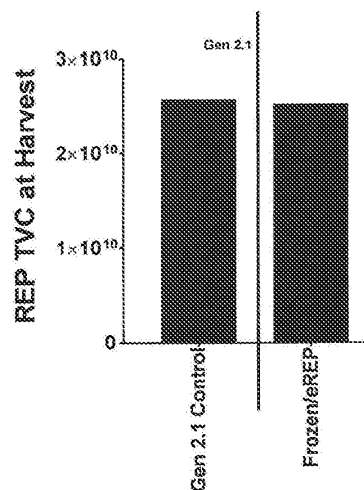


FIG. 14A



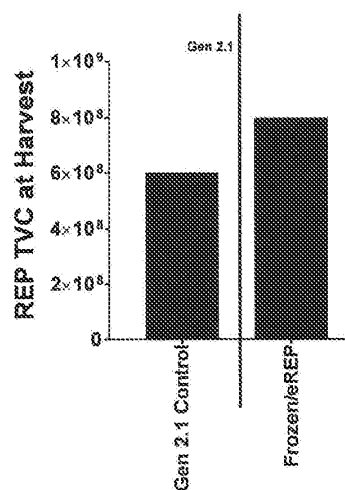
Total REP Yield	Gen 2 (Day 22)	Frozen/Early REP (Day 21)
Gen 2 Control	24.7E+09	-
Flash 0 min	-	22.6E+09
30 min inc.	-	19.7E+09
60 min inc.	-	21.2E+09

FIG. 14B



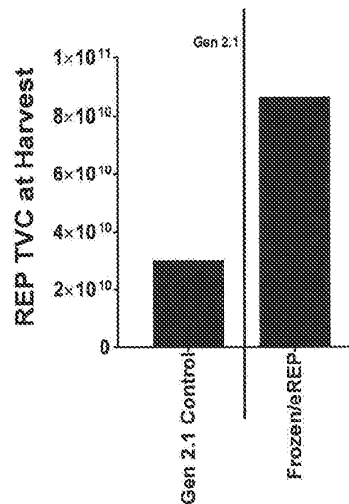
Total REP Yield	Gen 2 (Day 22)	Frozen/Early REP (Day 21)
Gen 2.1 Control	25.8E+09	-
Frozen/eREP	-	25.3E+09

FIG. 14C



Total REP Yield	Gen 2 (Day 22)	Frozen/Early REP (Day 21)
Gen 2.1 Control	0.6E+09	-
Frozen/eREP	-	0.8E+09

FIG. 14D



Total REP Yield	Gen 2 (Day 22)	Frozen/Early REP (Day 21)
Gen 2.1 Control	30E+09	-
Frozen/eREP	-	87E+09

FIG. 14E

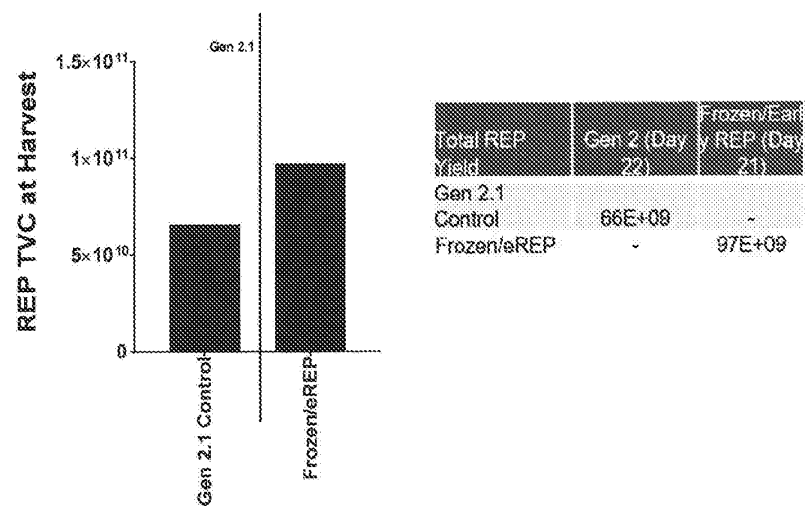


FIG. 15

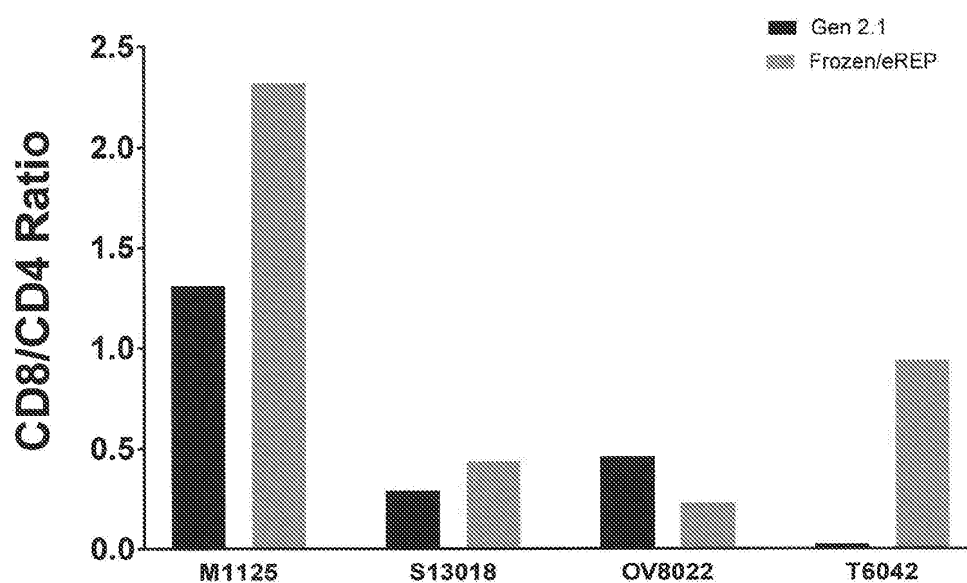


FIG. 16A

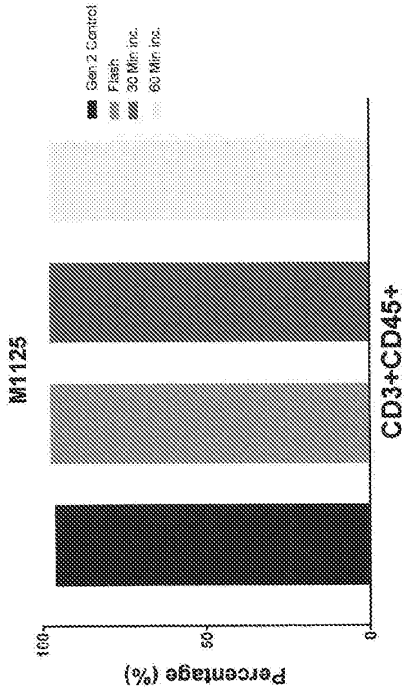


FIG. 16C

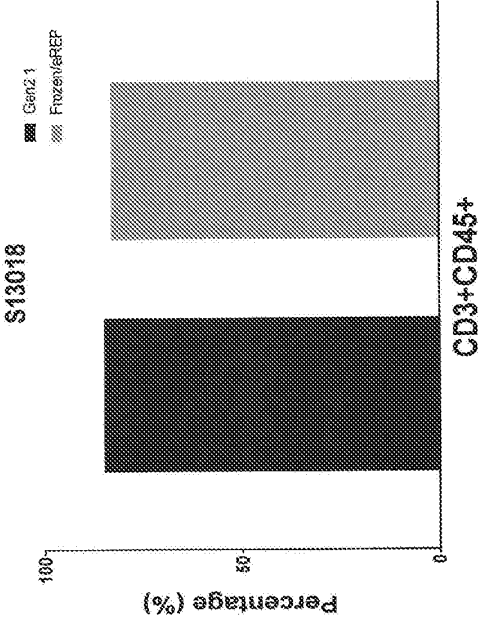


FIG. 16B

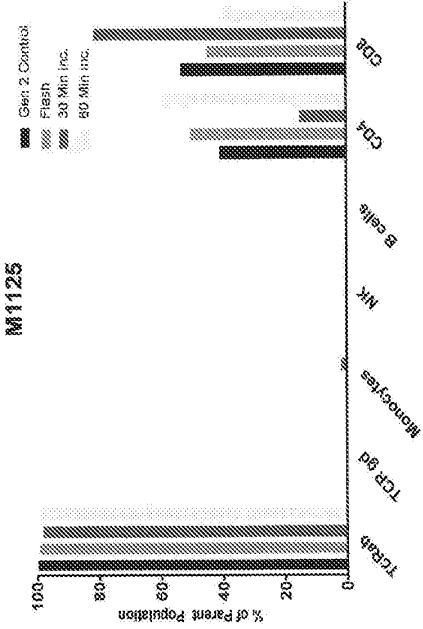


FIG. 16D

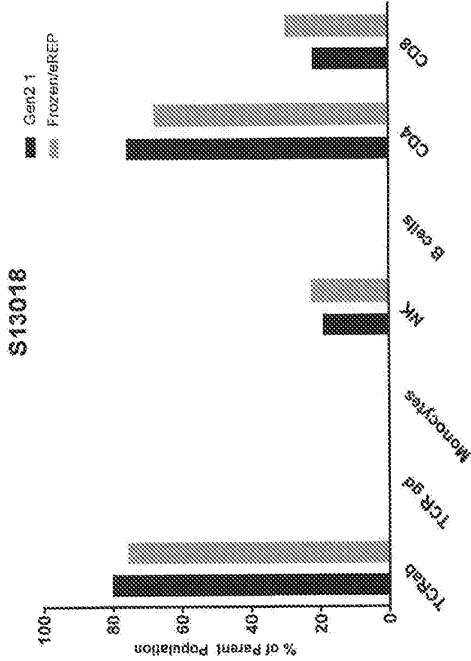


FIG. 16G

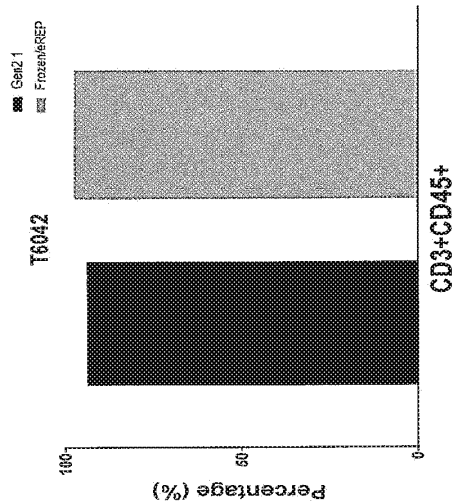


FIG. 16E

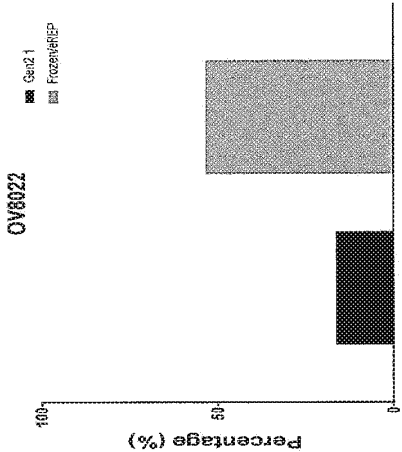


FIG. 16H

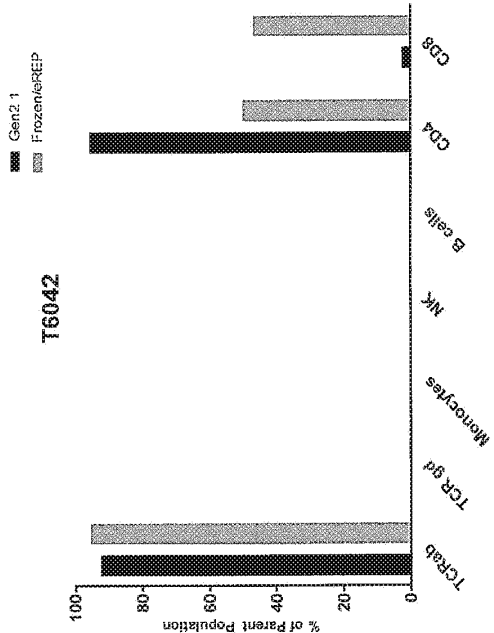
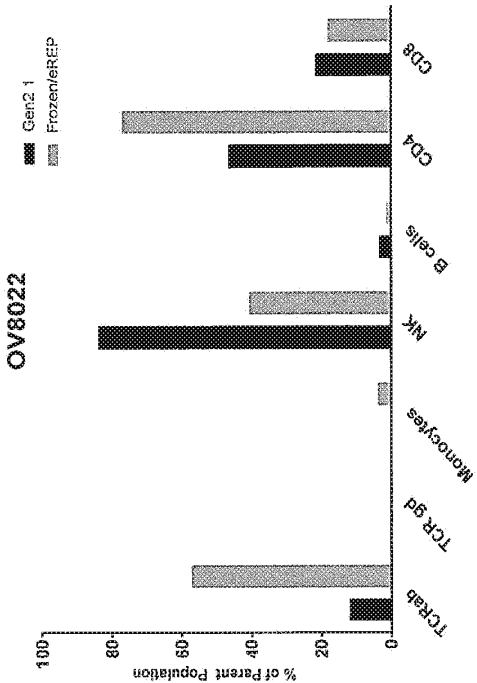
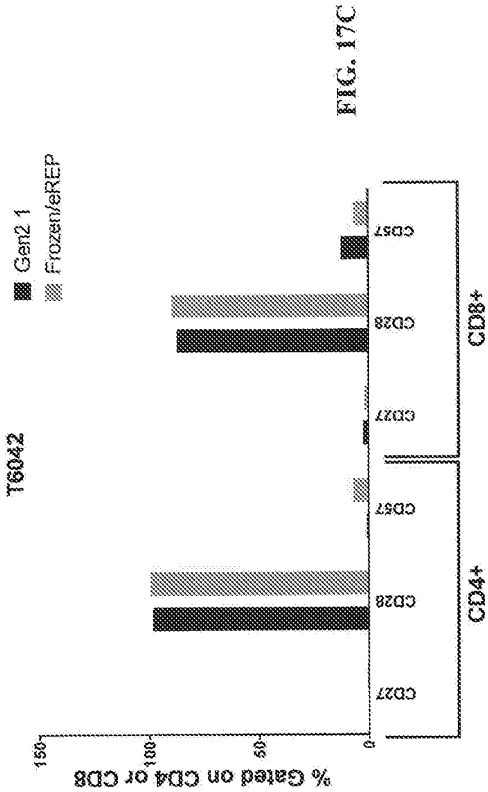
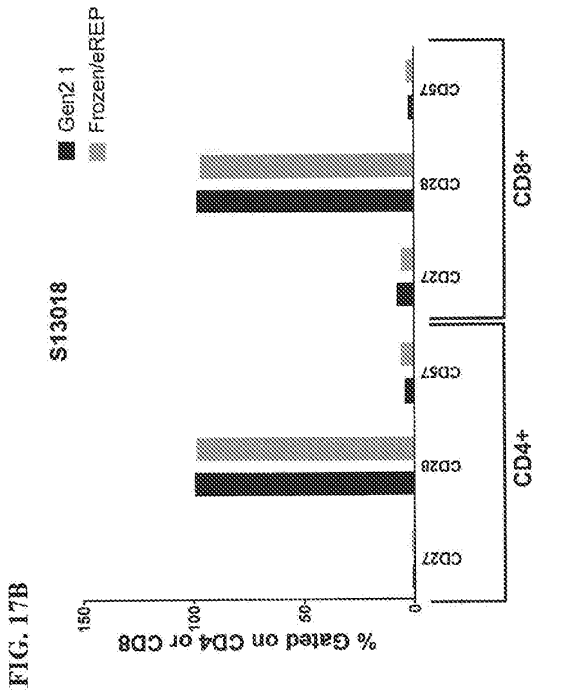
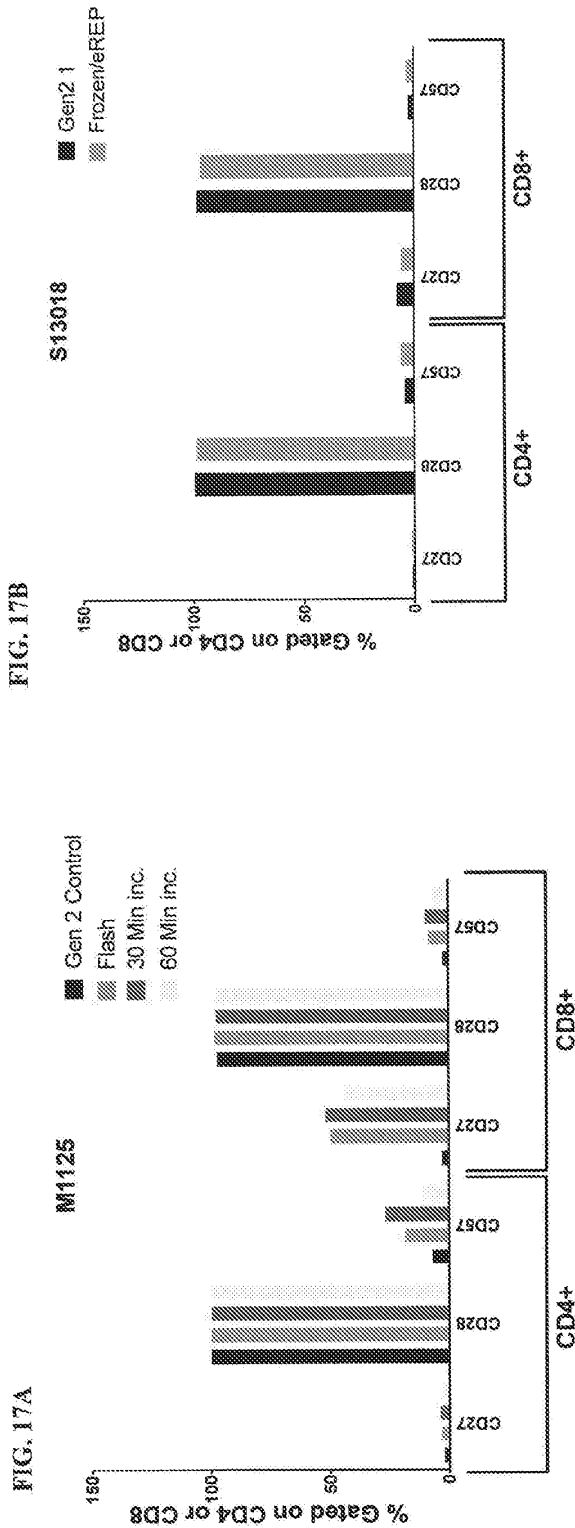


FIG. 16F





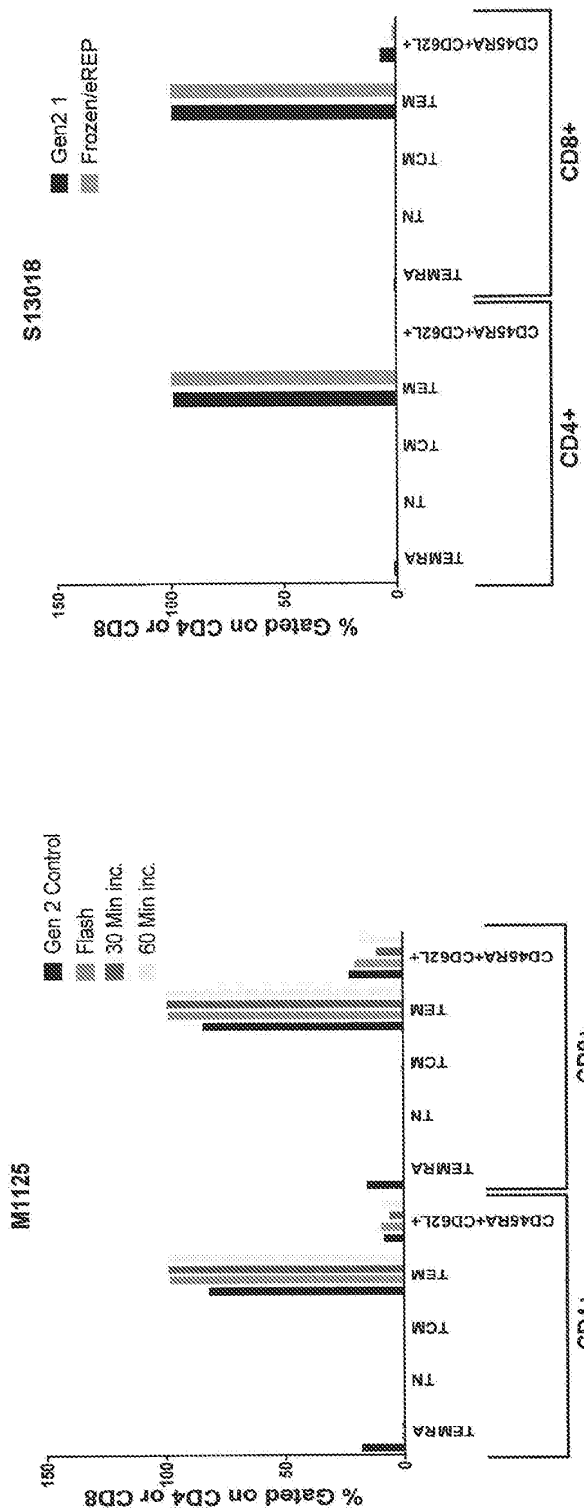


FIG. 18A

T6042

FIG. 18B

22/30

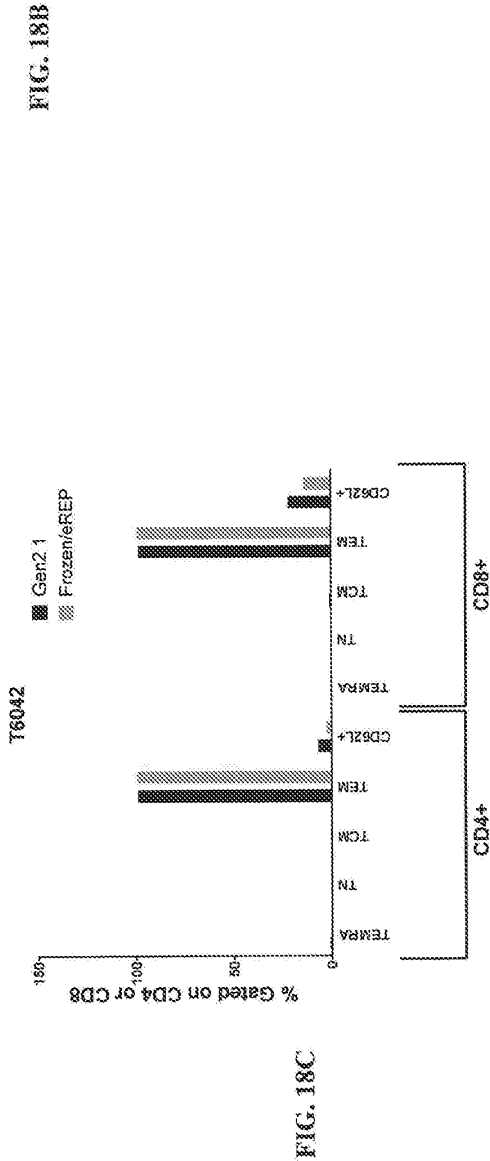


FIG. 18C

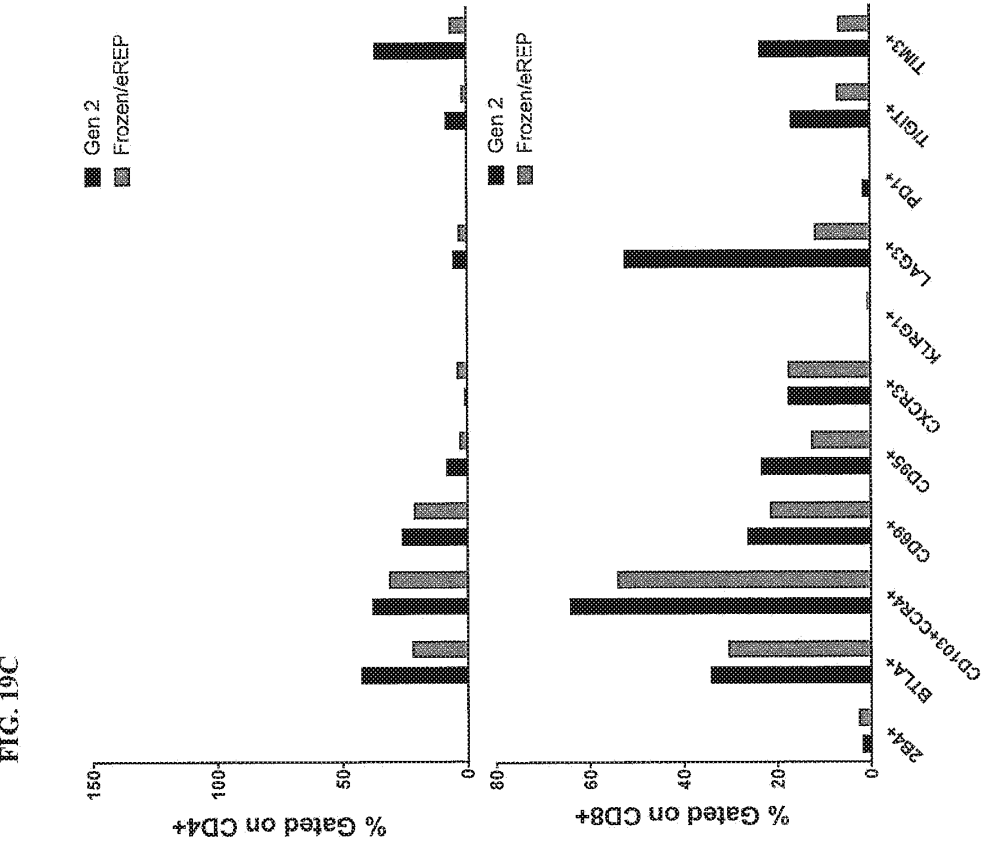


FIG. 20B

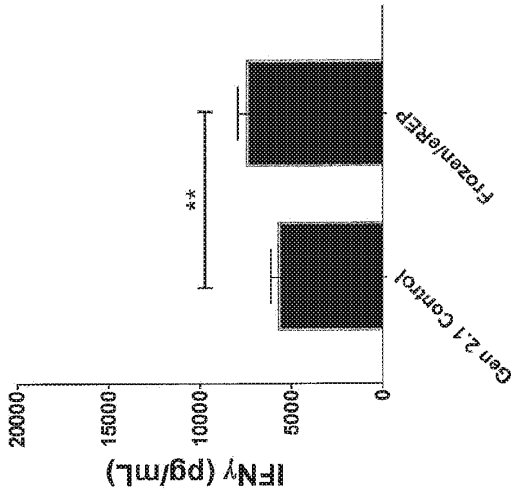


FIG. 20A

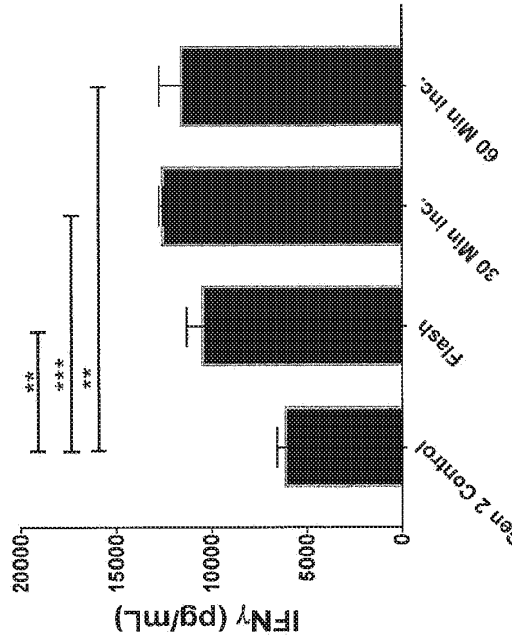
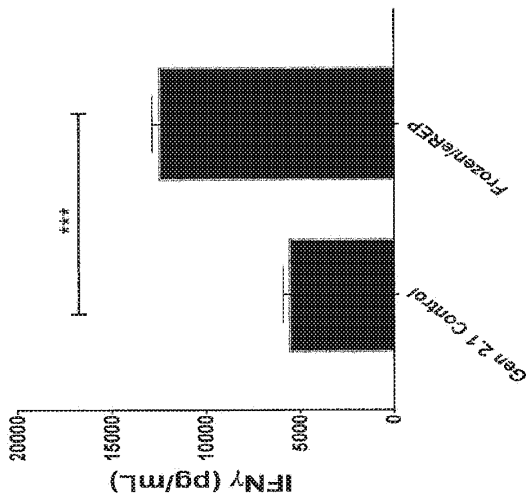
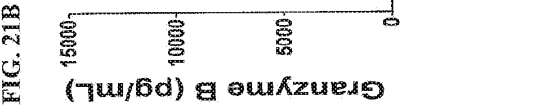
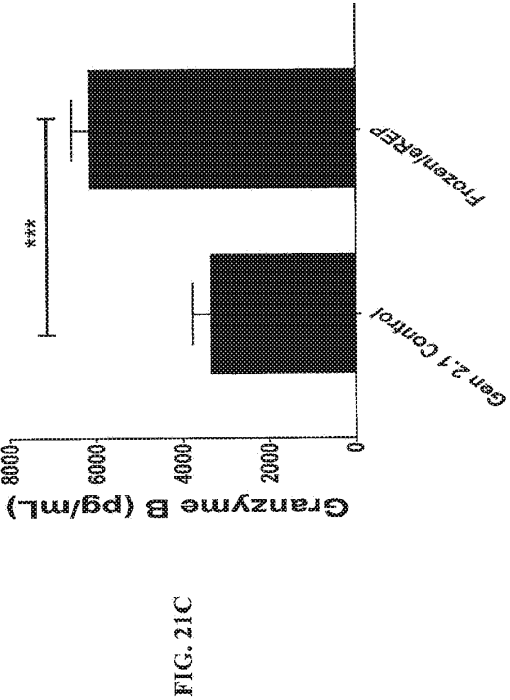
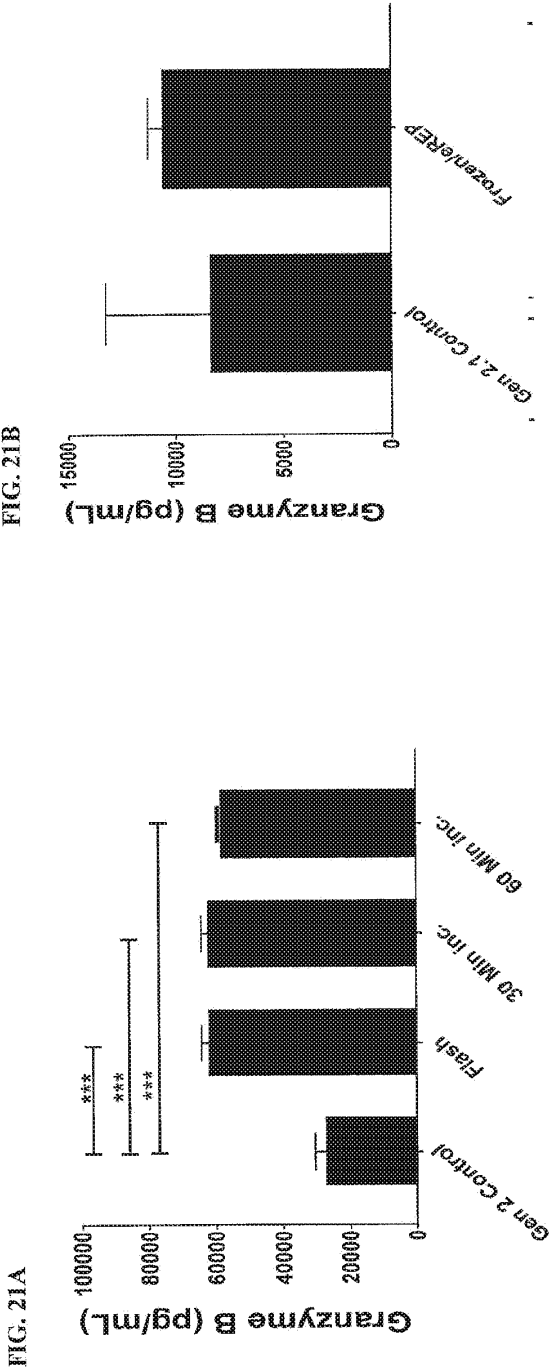
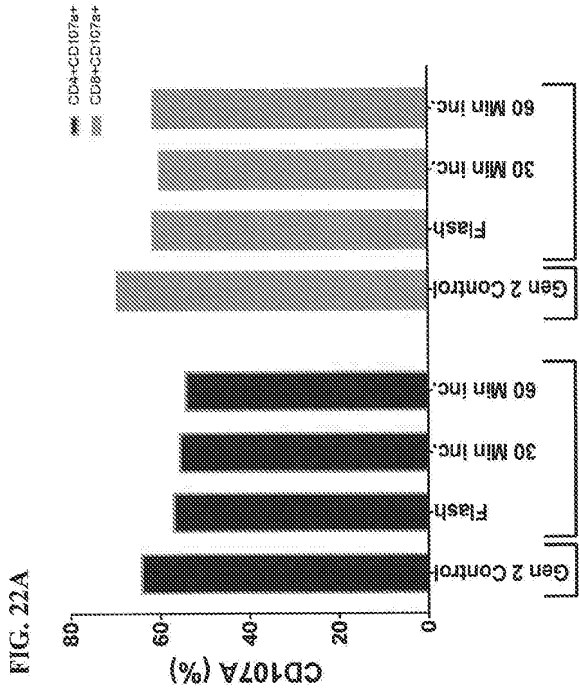
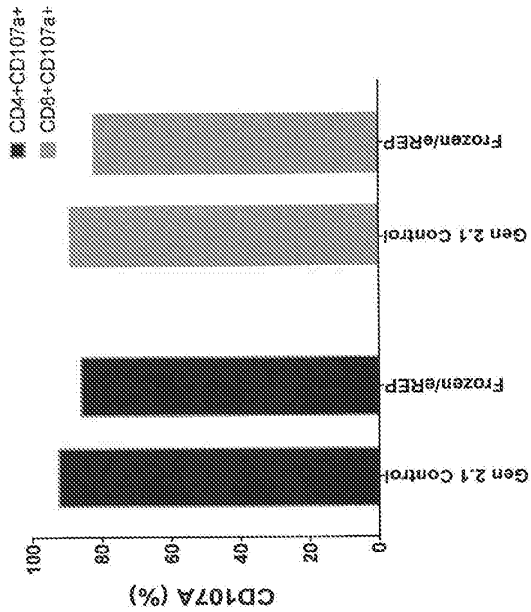
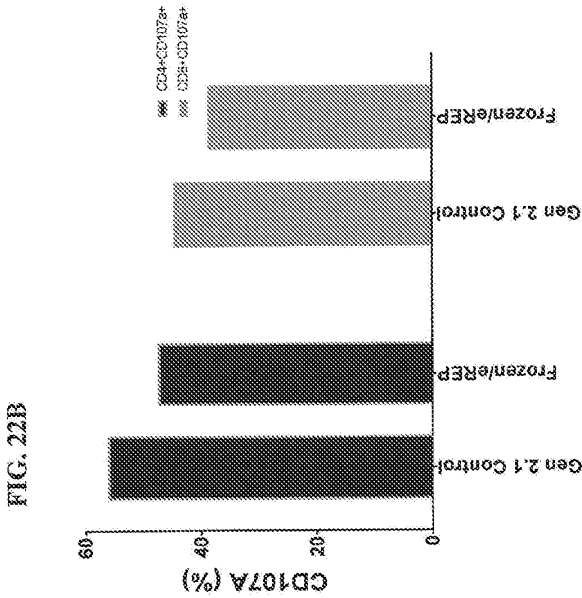
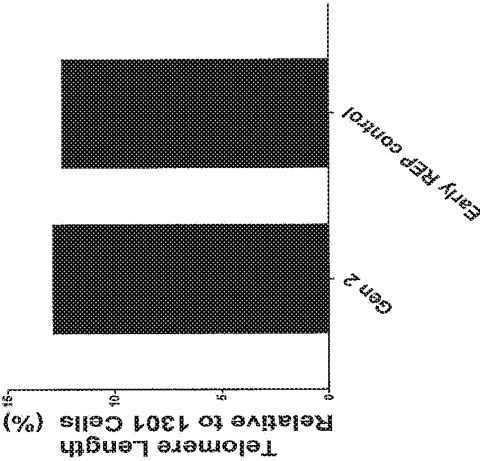
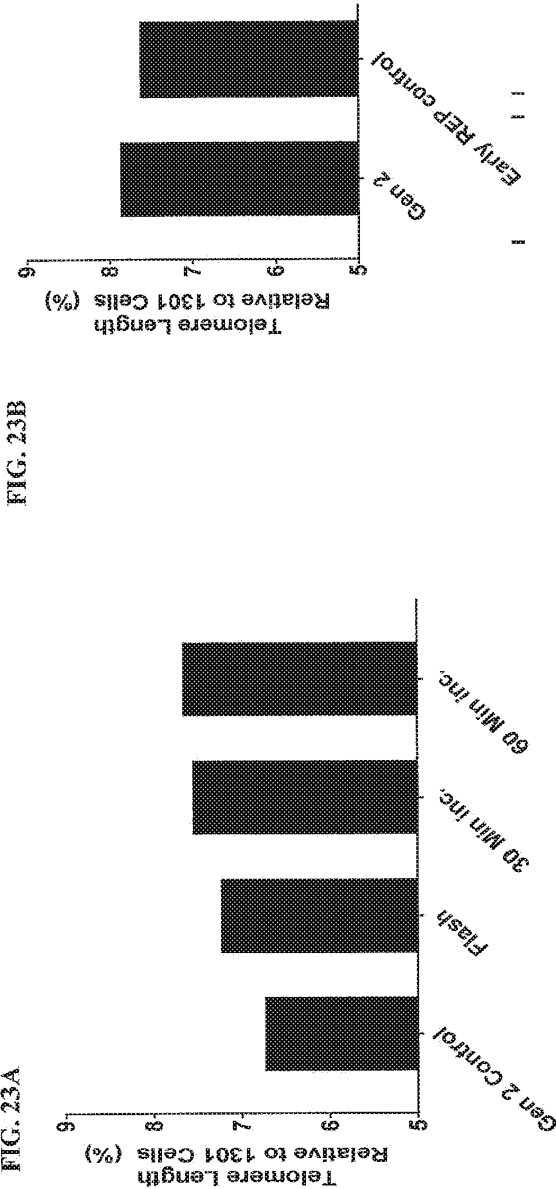


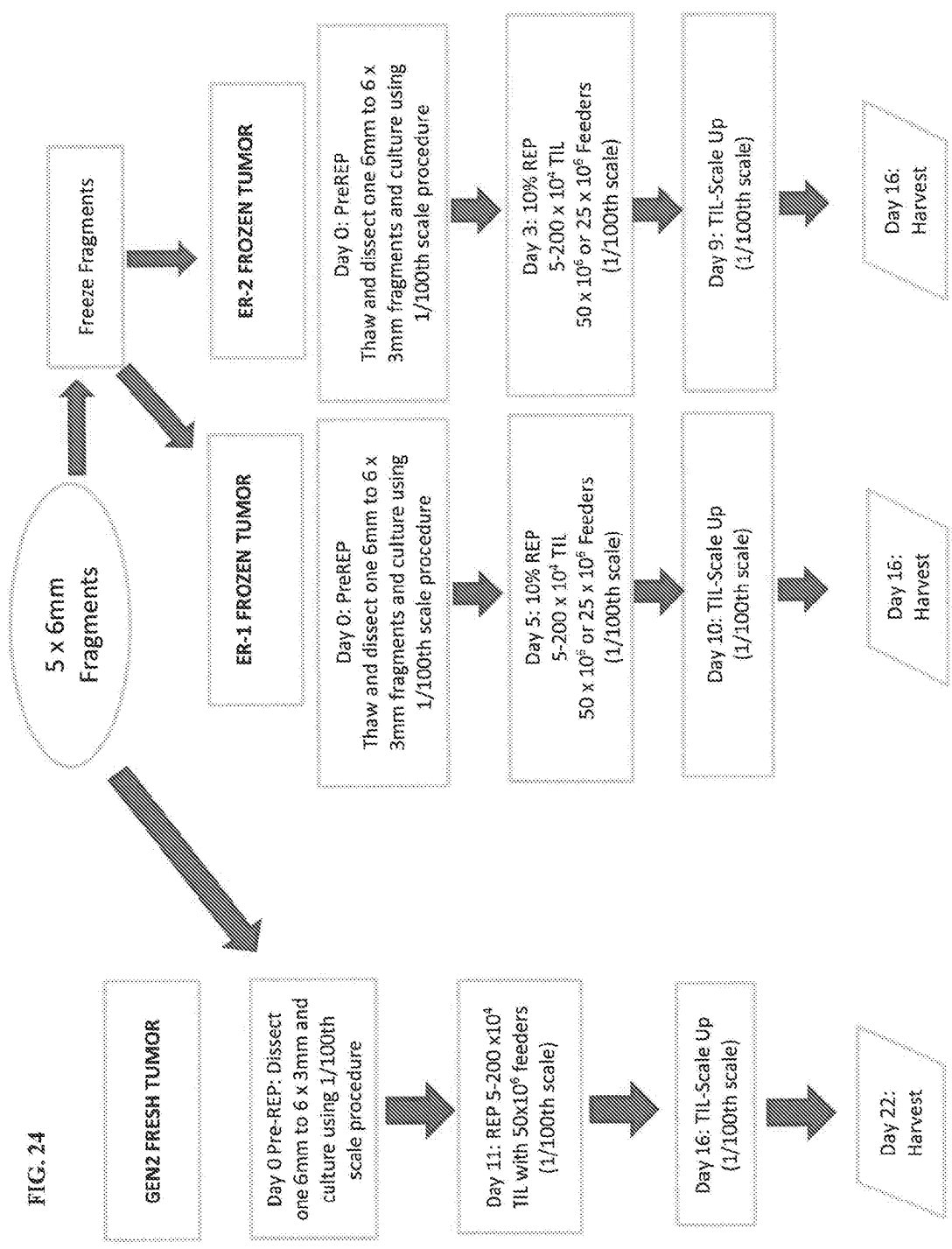
FIG. 20C











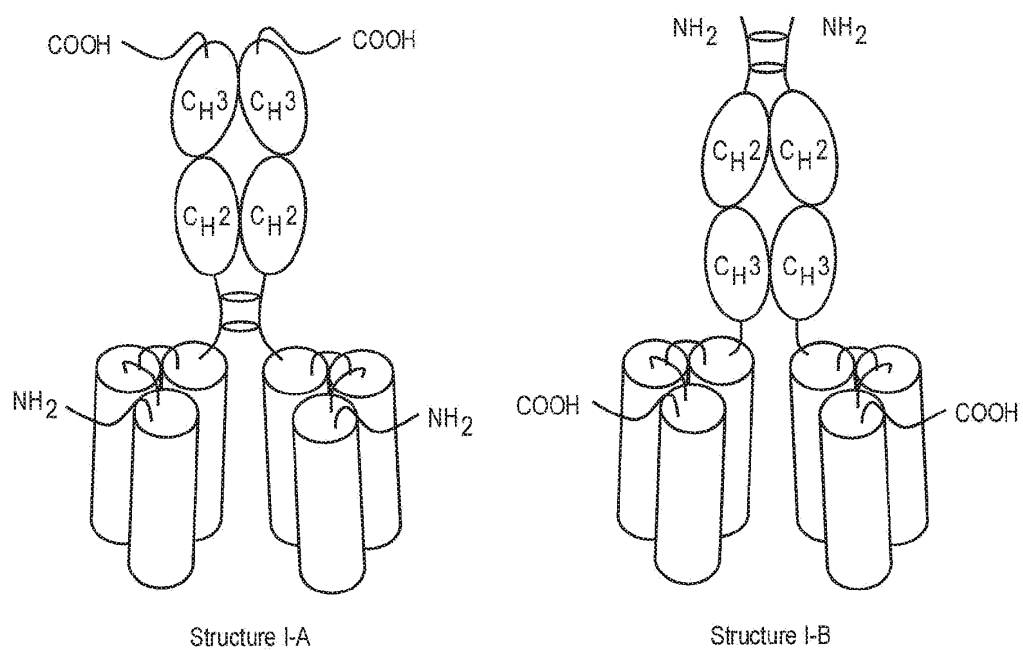


FIG. 25