

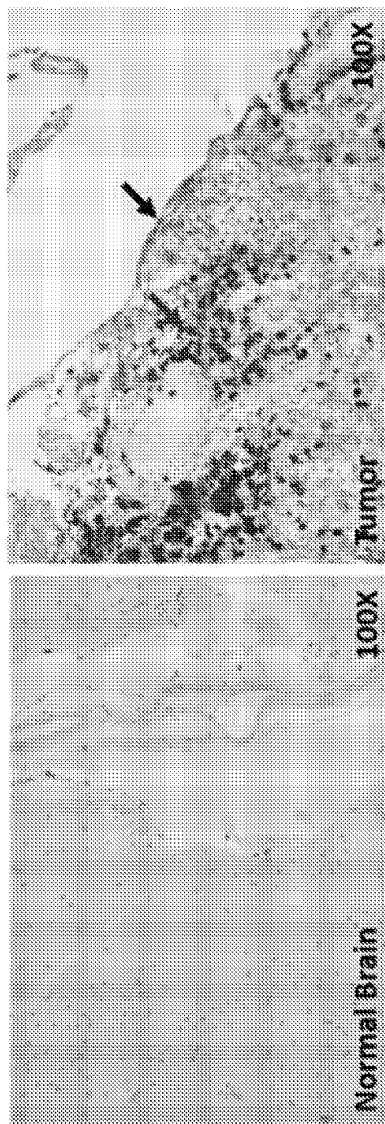


FIG. 1A

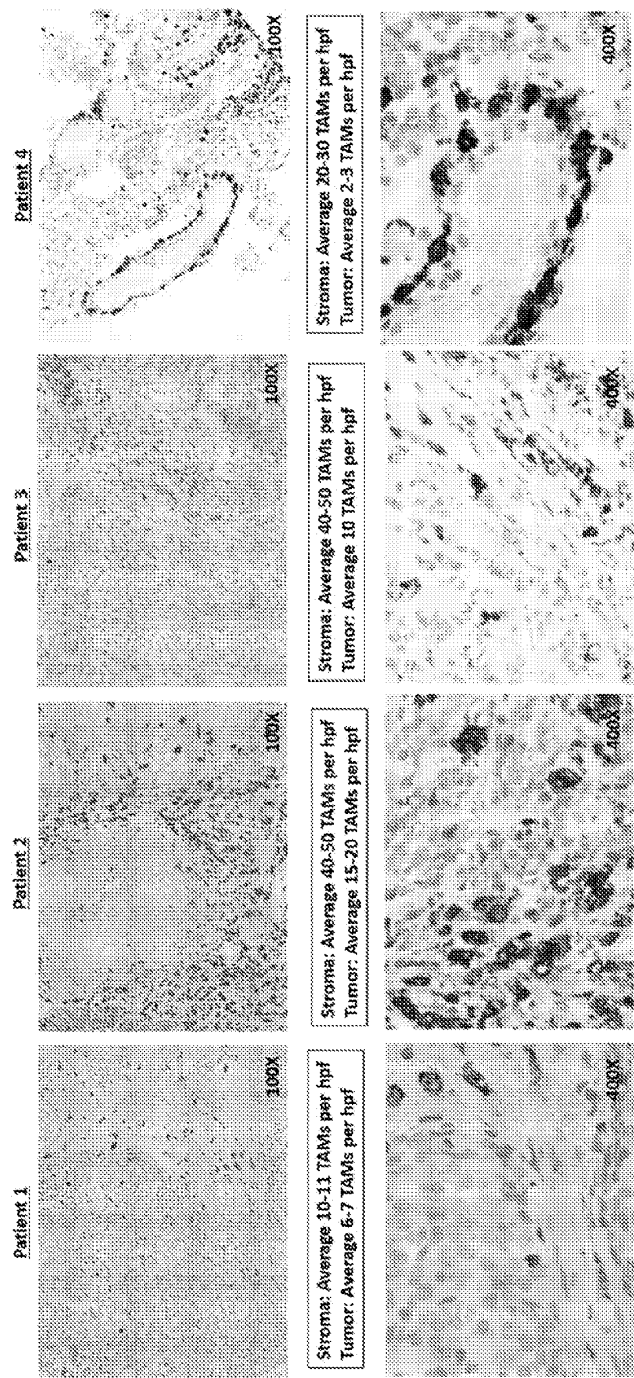


FIG. 1B

Stroma vs Tumor:  $p=0.022$  (Paired T-test)

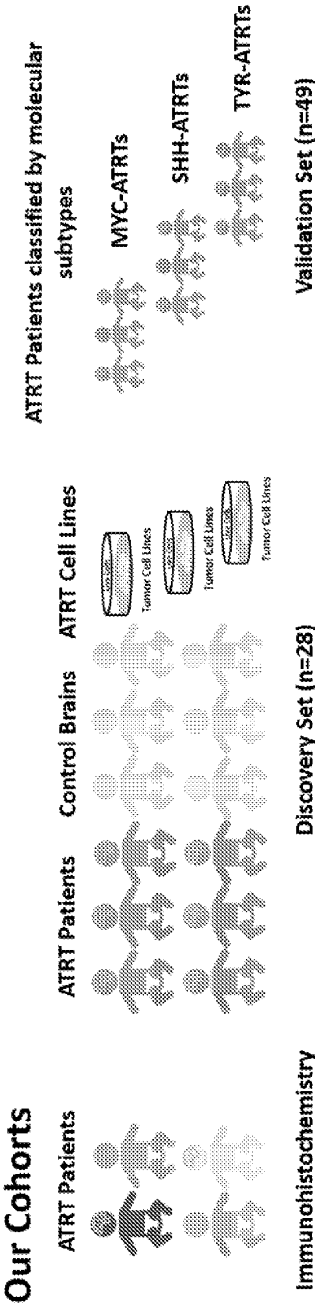


FIG. 1C (continued)

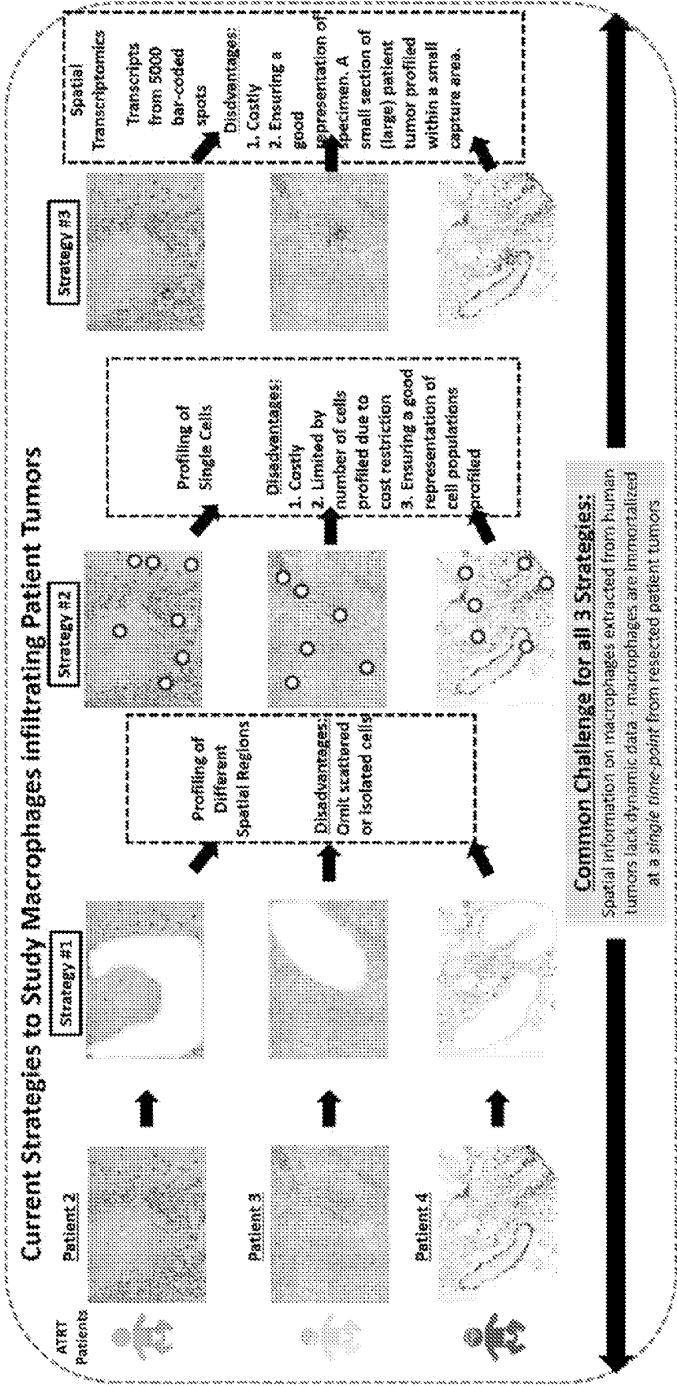


FIG. 1C



Generation of Secretome

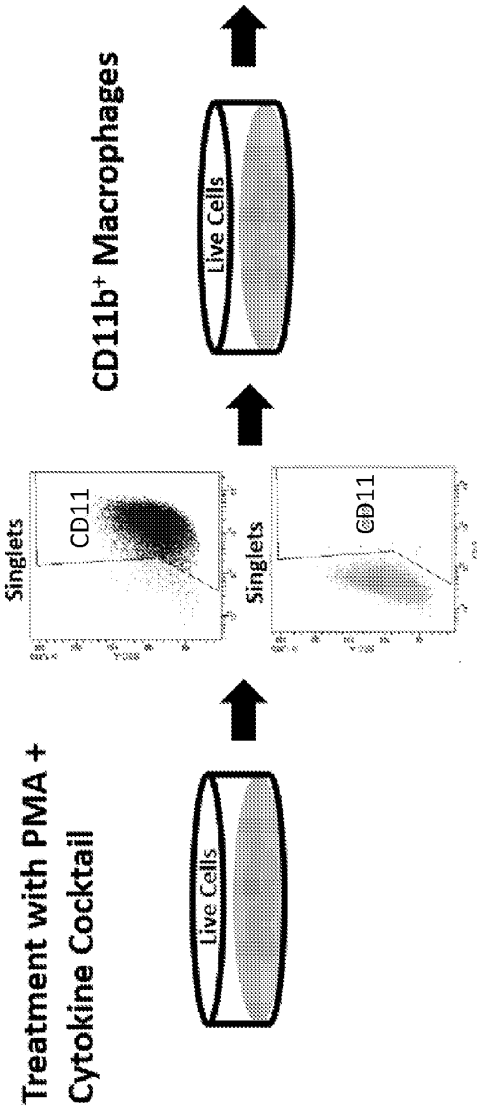


FIG. 2A

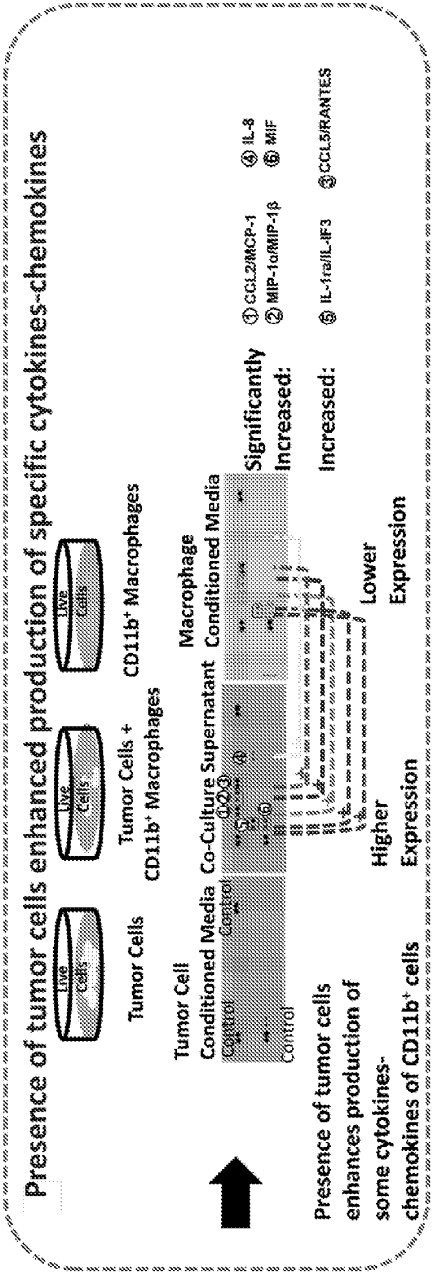
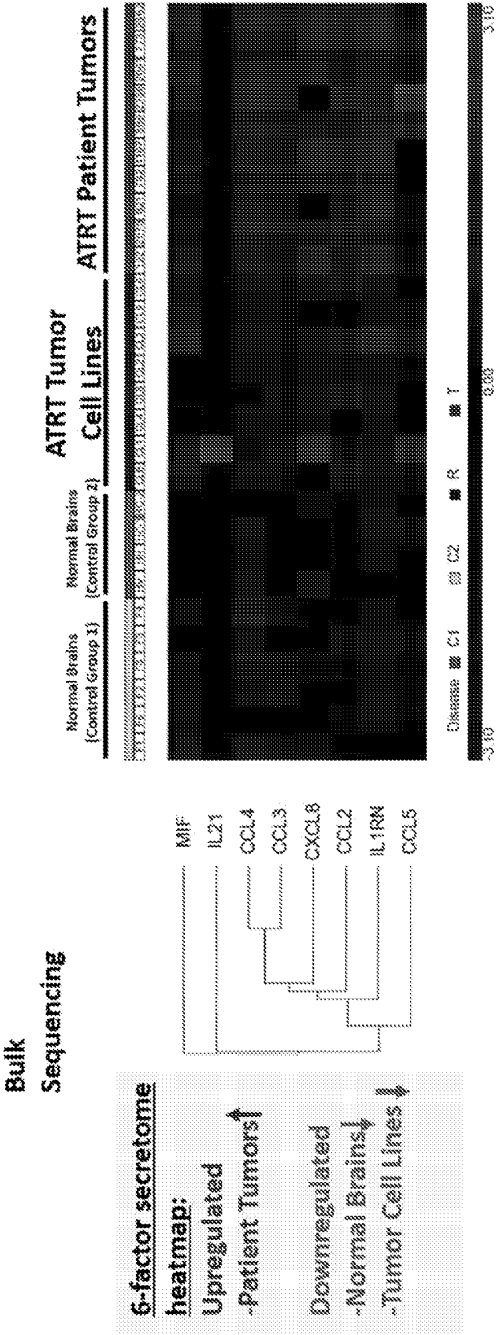


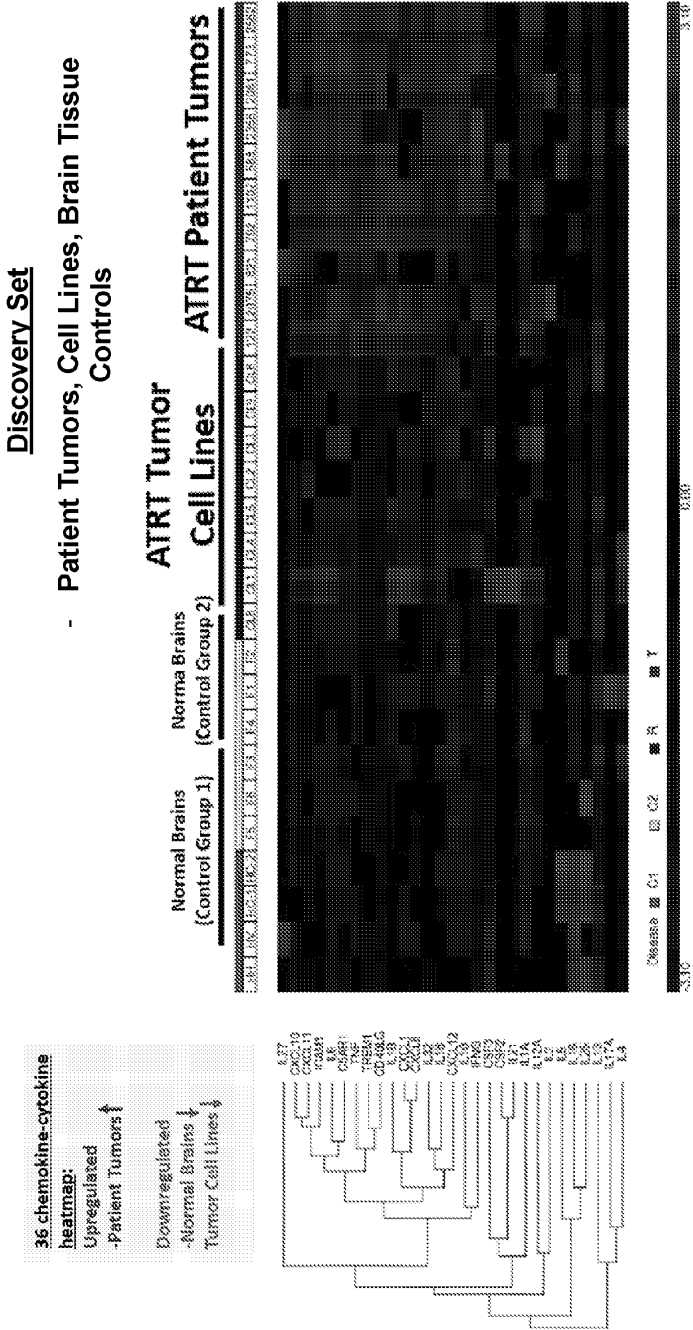
FIG. 2B

6-factor secretome enriched among MYC-ATRT & TYR-ATRT subtypes

Discovery Set  
-- Patient Tumors, Cell Lines, Brain Tissue Controls  
(RNA-Seq; n=28)



6-factor secretome enriched among MYC-ATRT & TYR-ATRT subtypes



6-factor secretome enriched among MYC-ATRT & TYR-ATRT subtypes

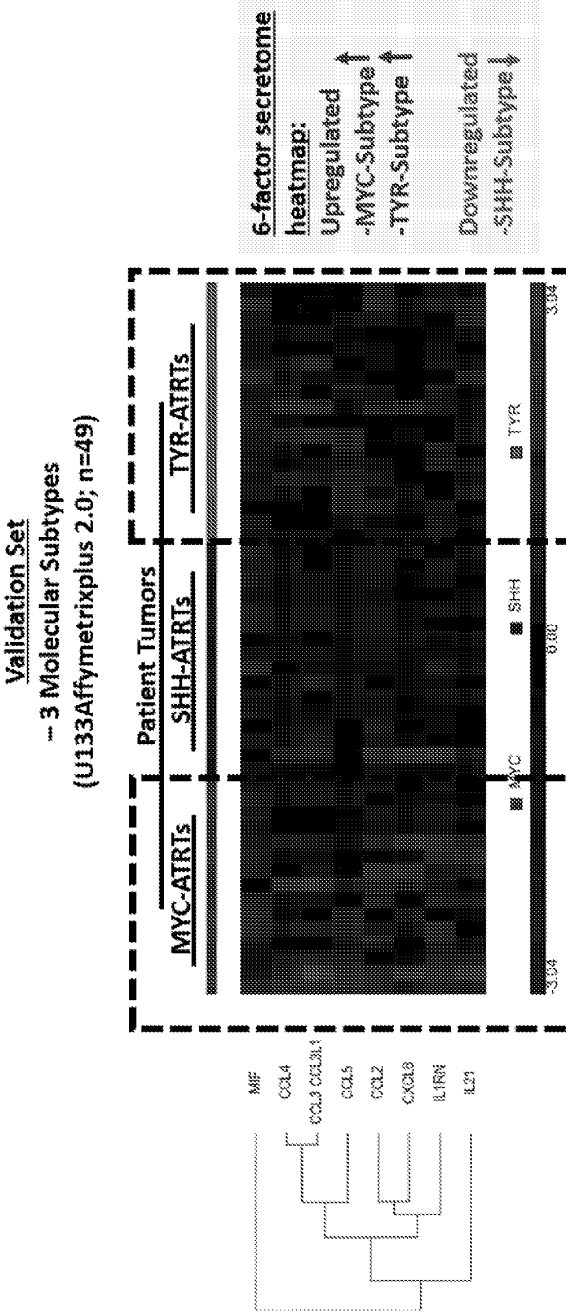


FIG. 2D (continued)

6-factor secretome enriched among MYC-ATRT & TYR-ATRT subtypes

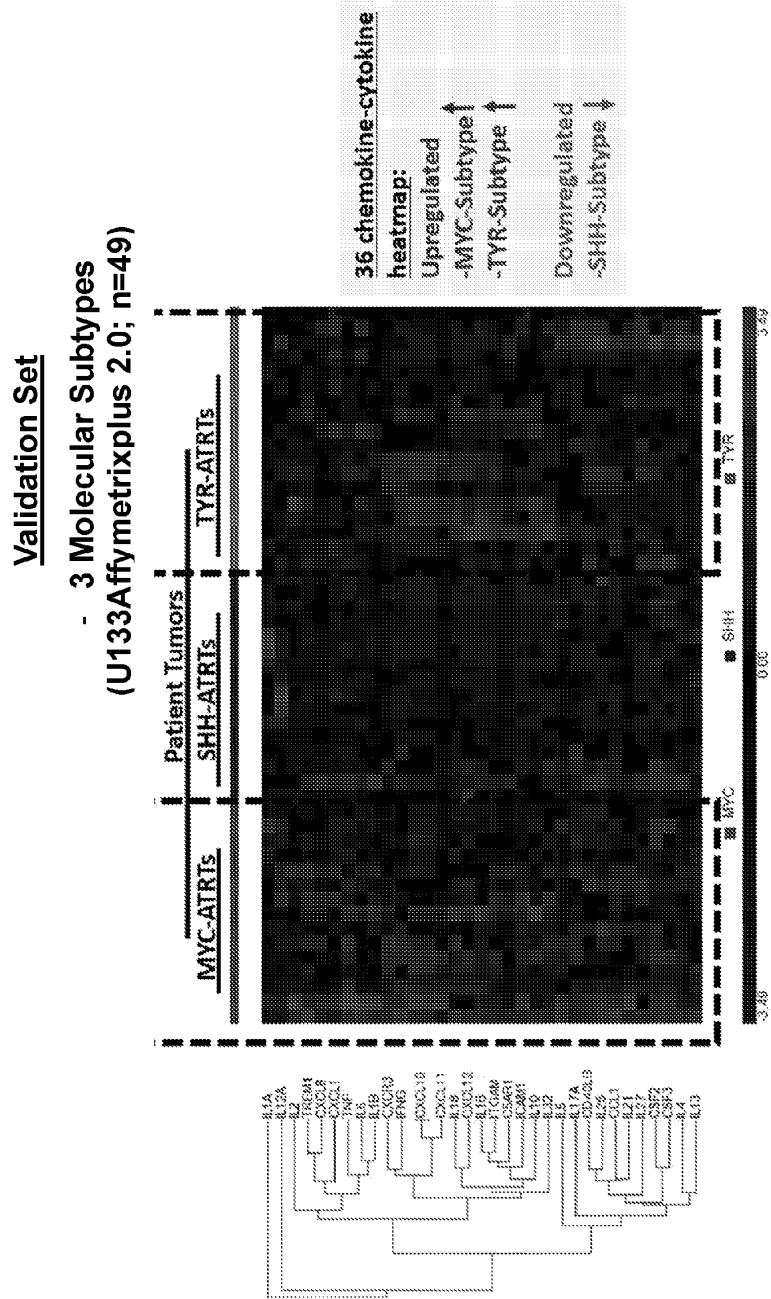
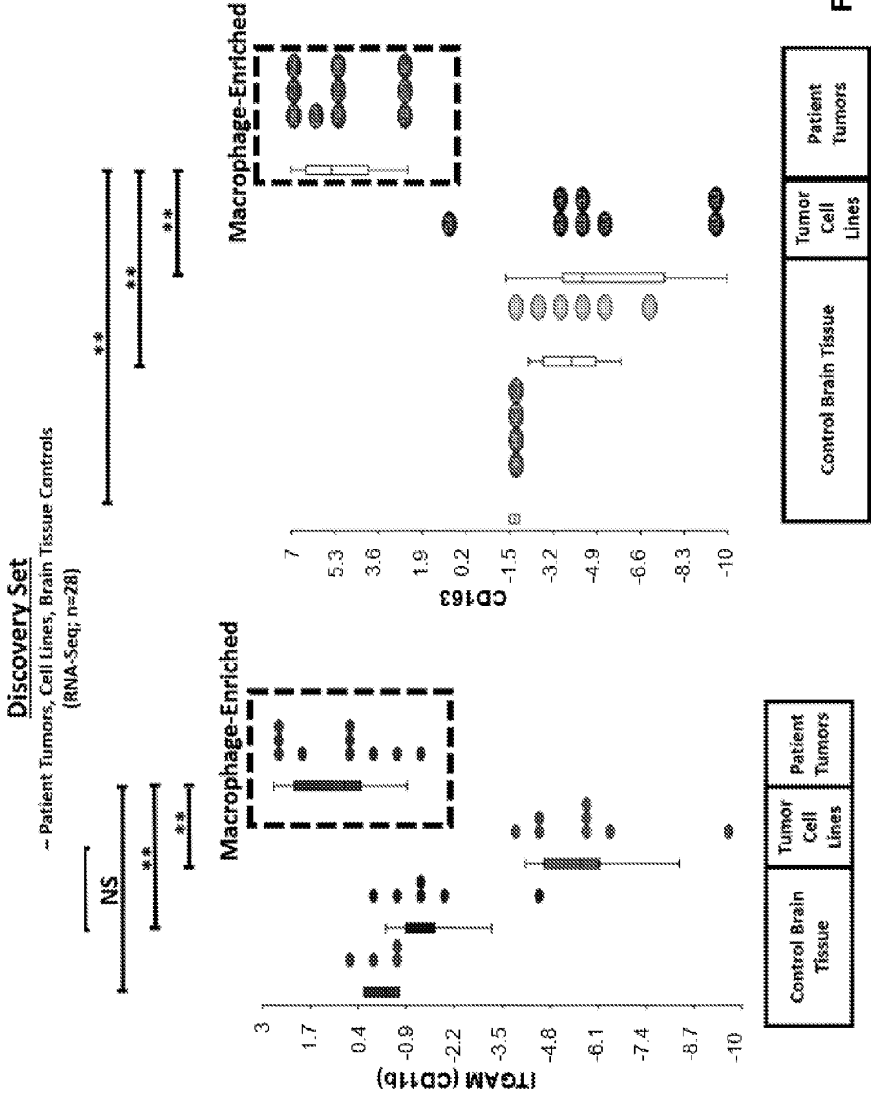


FIG. 2D

Macrophage enrichment patterns matched tumor subtypes enriched in 6-Factor secretome



Macrophage enrichment patterns matched tumor subtypes enriched in 6-Factor secretome

Validation Set

— 3 Molecular Subtypes (U133Affymetrixplus 2.0; n=49)

p-value (Anova Test)  
\*\*: SHH vs MYC/TYR  
NS: TYR vs SHH/MYC  
NS: MYC vs SHH/TYR

p-value (Anova Test)  
\*\*: SHH vs MYC/TYR  
NS: TYR vs SHH/MYC  
NS: MYC vs SHH/TYR

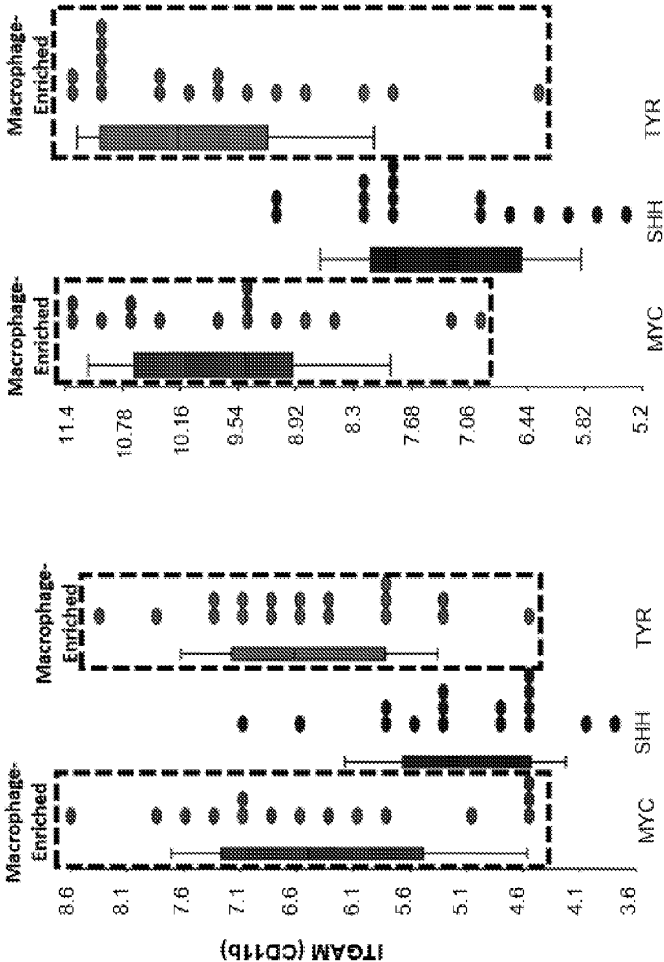
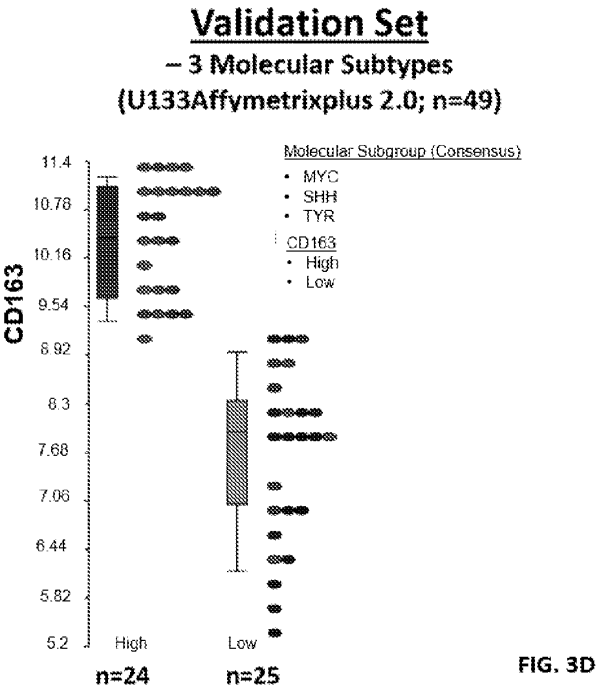


FIG. 3B





Macrophage enrichment patterns matched tumor subtypes enriched in 6-Factor secretome



Macrophage enrichment patterns matched tumor subtypes enriched in  
6-Factor secretome

Validation Set

— 3 Molecular Subtypes  
(U133Affymetrixplus 2.0; n=49)

Top 10 significant pathways

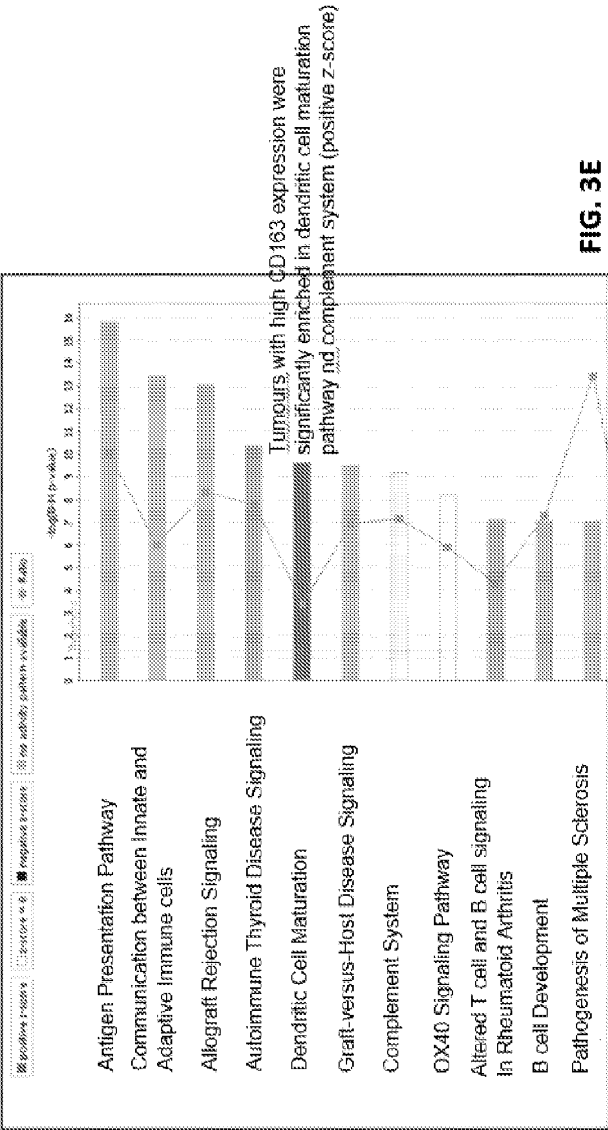
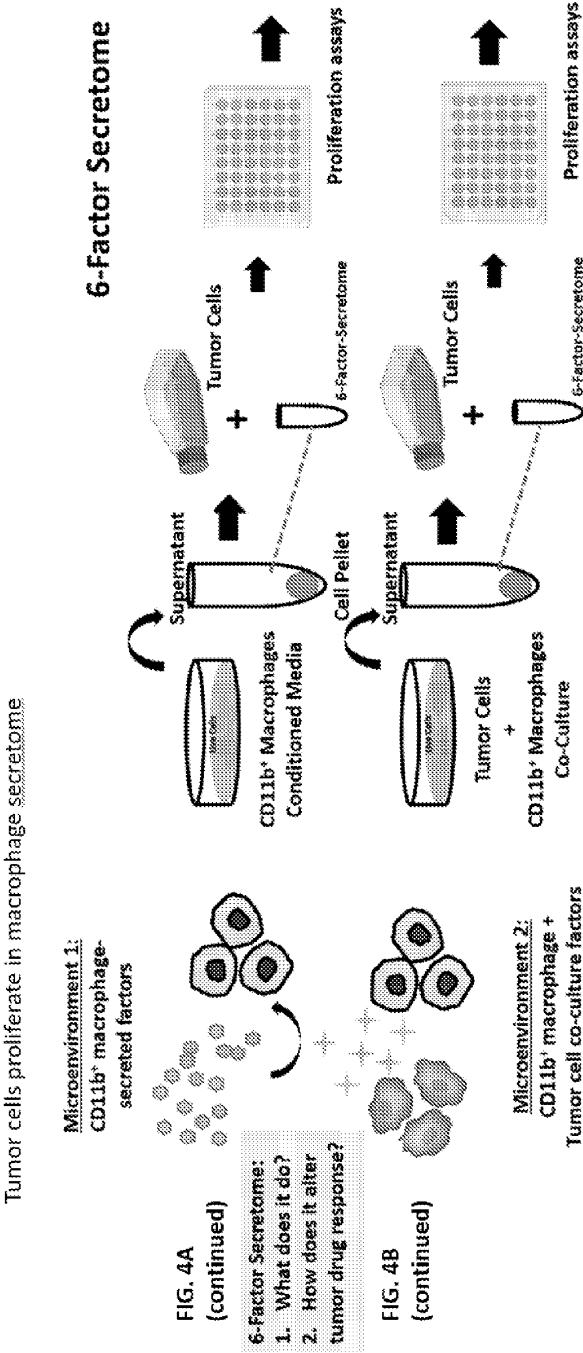
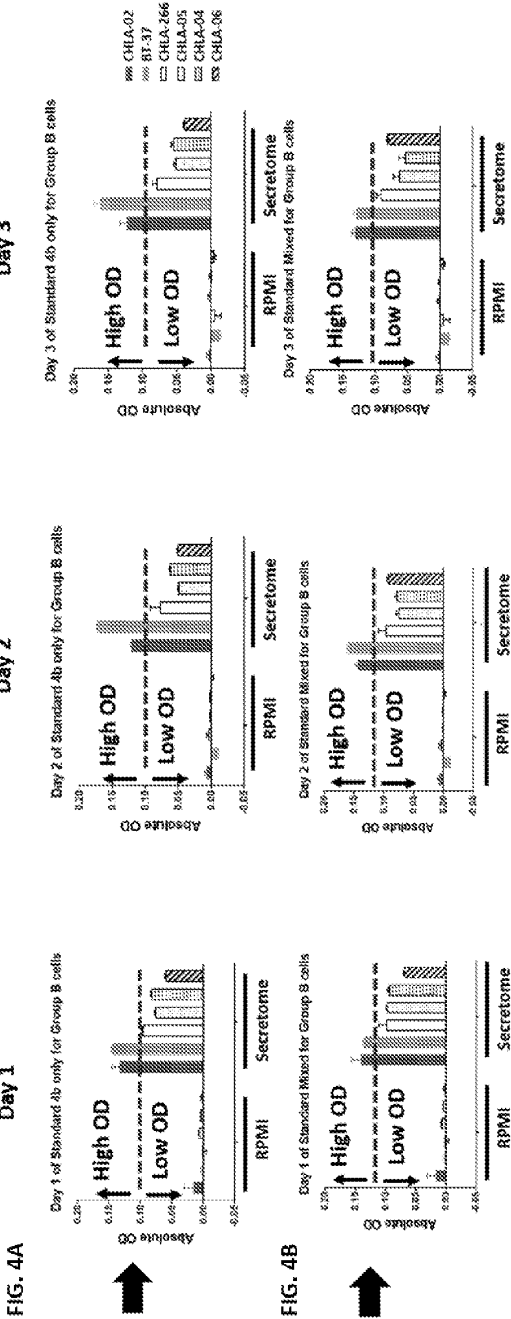


FIG. 3E



Tumor cells proliferate in macrophage secretome

**Effects of 6-Factor Secretome on Tumor Cell Proliferation**  
**(Panel of 6 ATRT Cell Lines)**



Cancer cells during nutrient-poor state

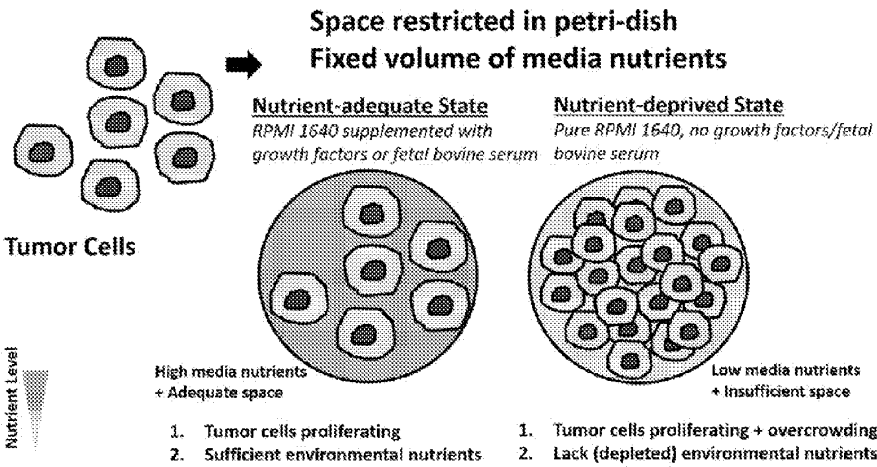


FIG. 4C (continued)

Macrophage secretome as an alternative resource during nutrient-stress

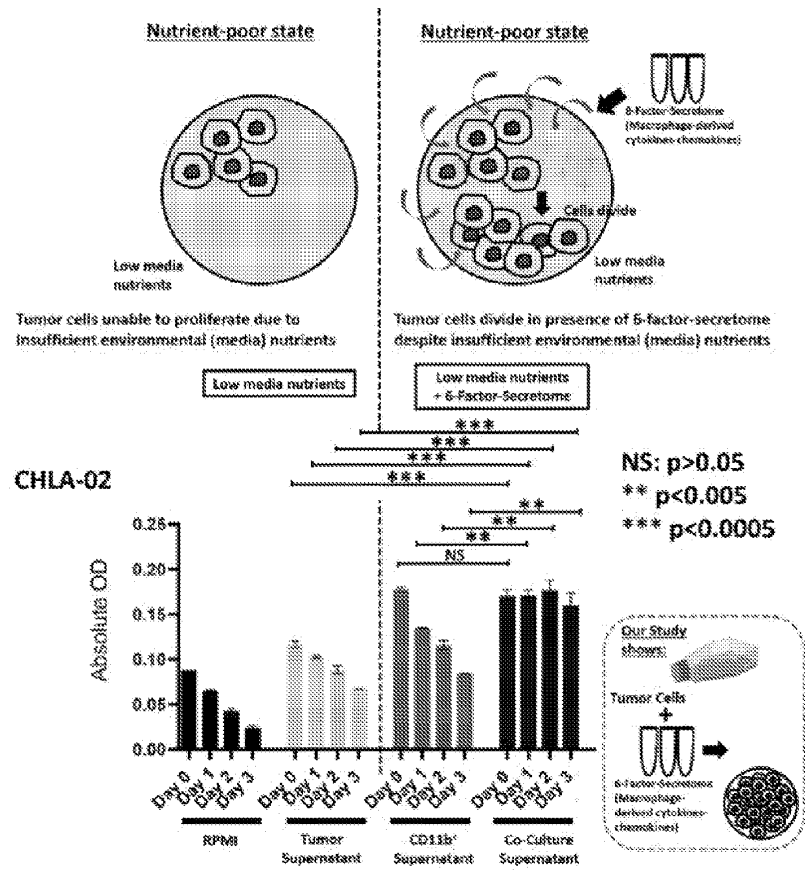


FIG. 4C

## CHLA-02

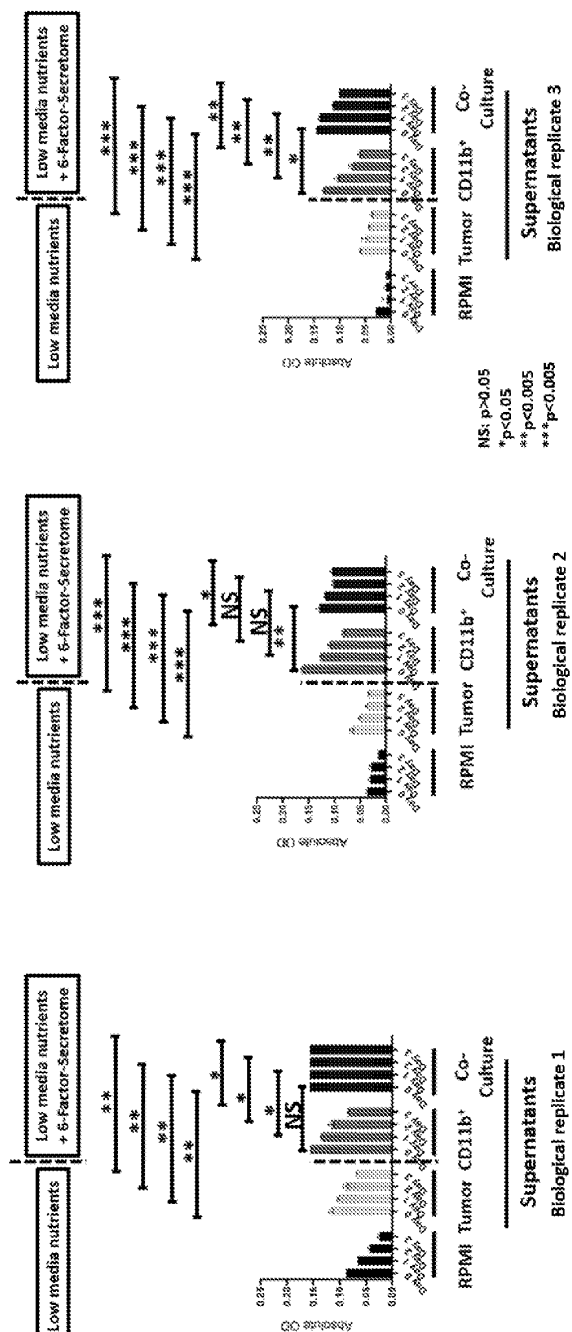


FIG. 4D (continued)



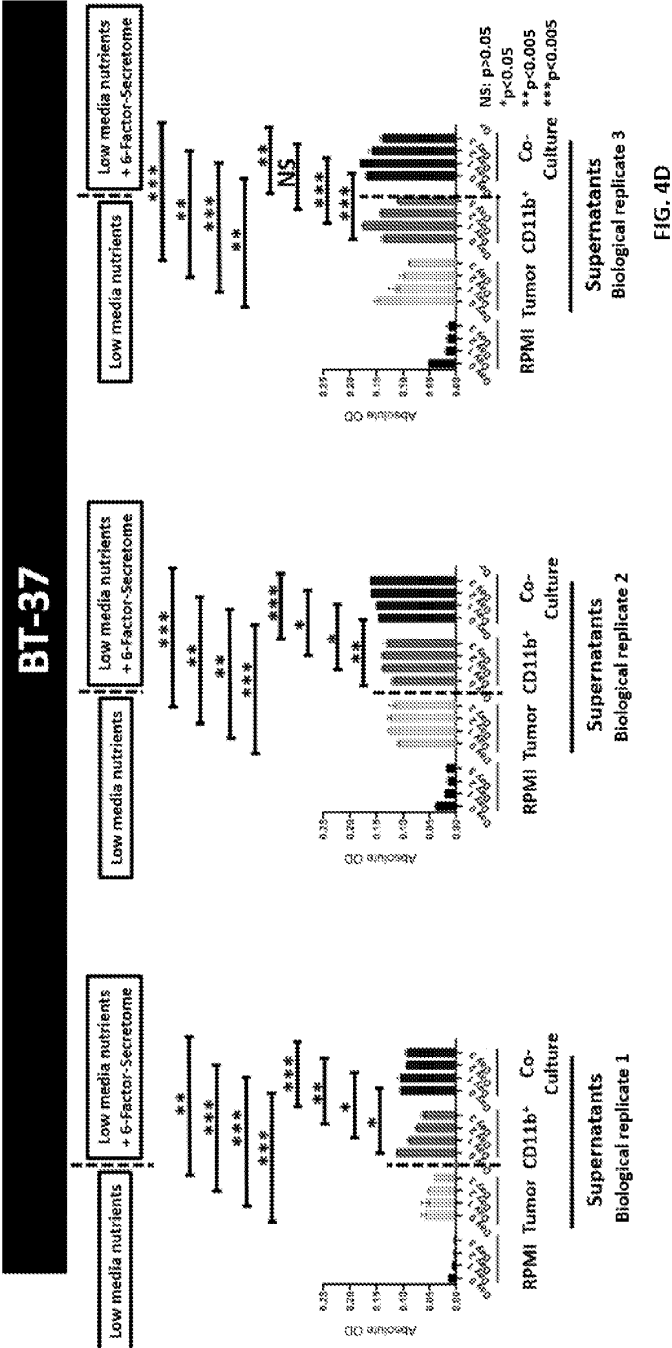


FIG. 4D

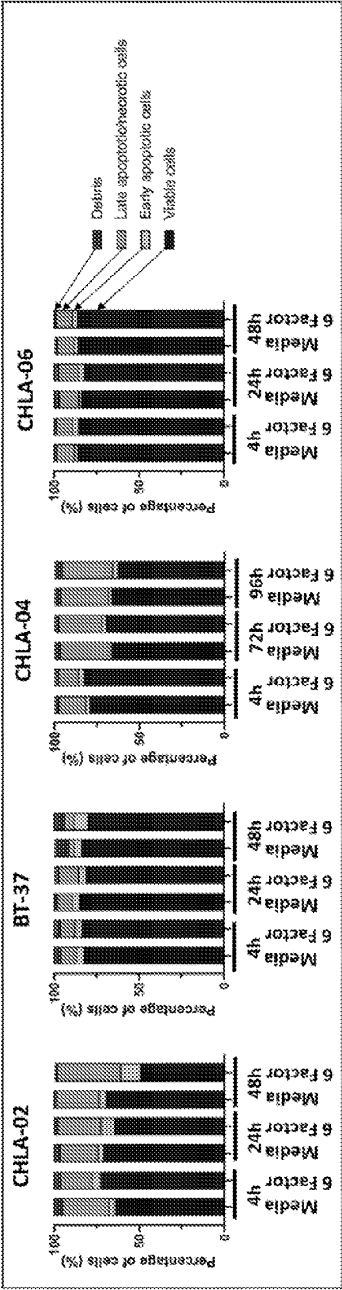


FIG. 4E

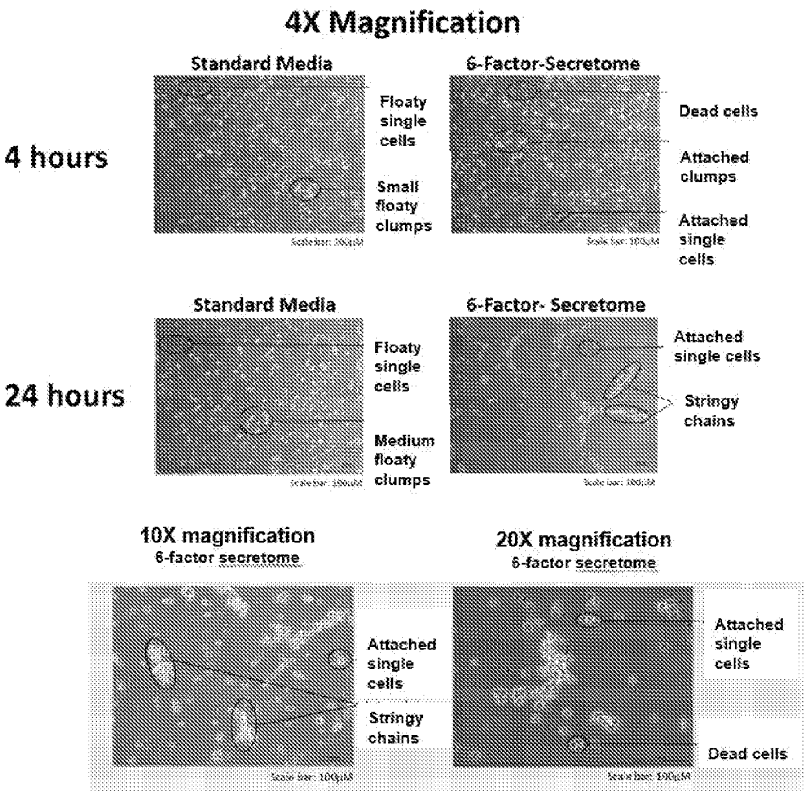


FIG. 4F

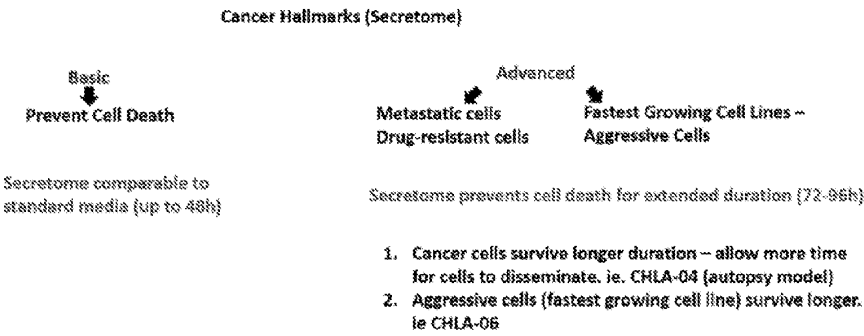
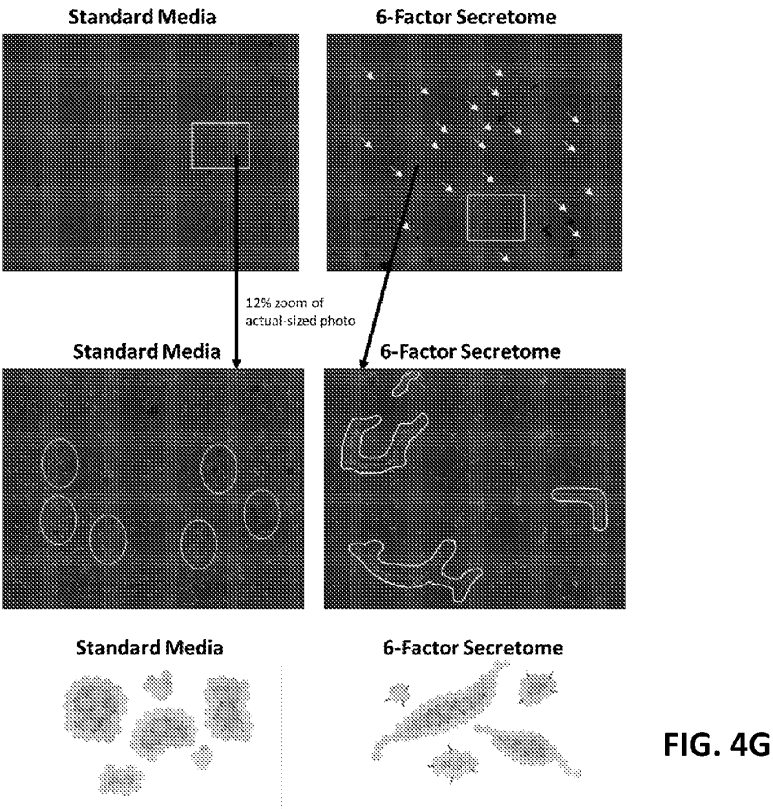


FIG. 4H

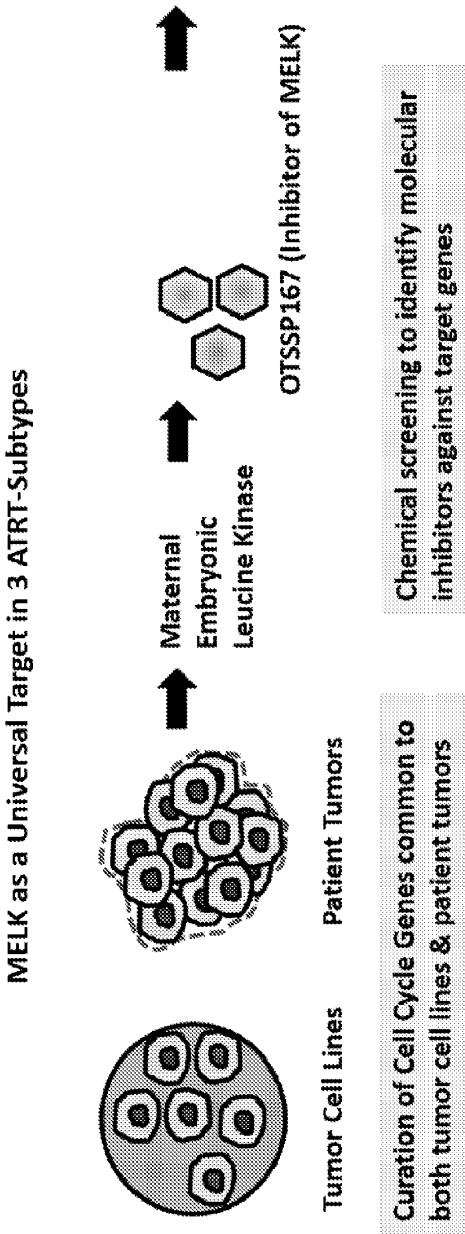
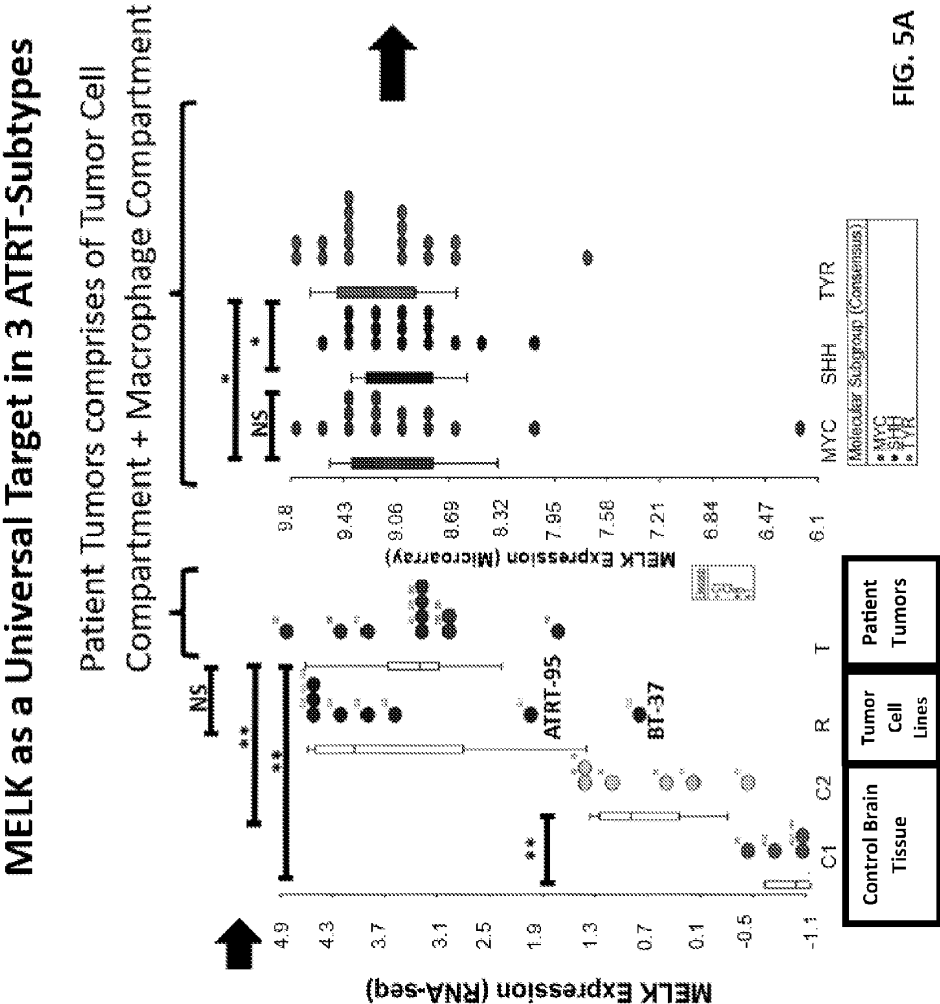


FIG. 5A (continued)



MELK inhibitor (OTSSP167) is effective against a panel of 6 cell lines

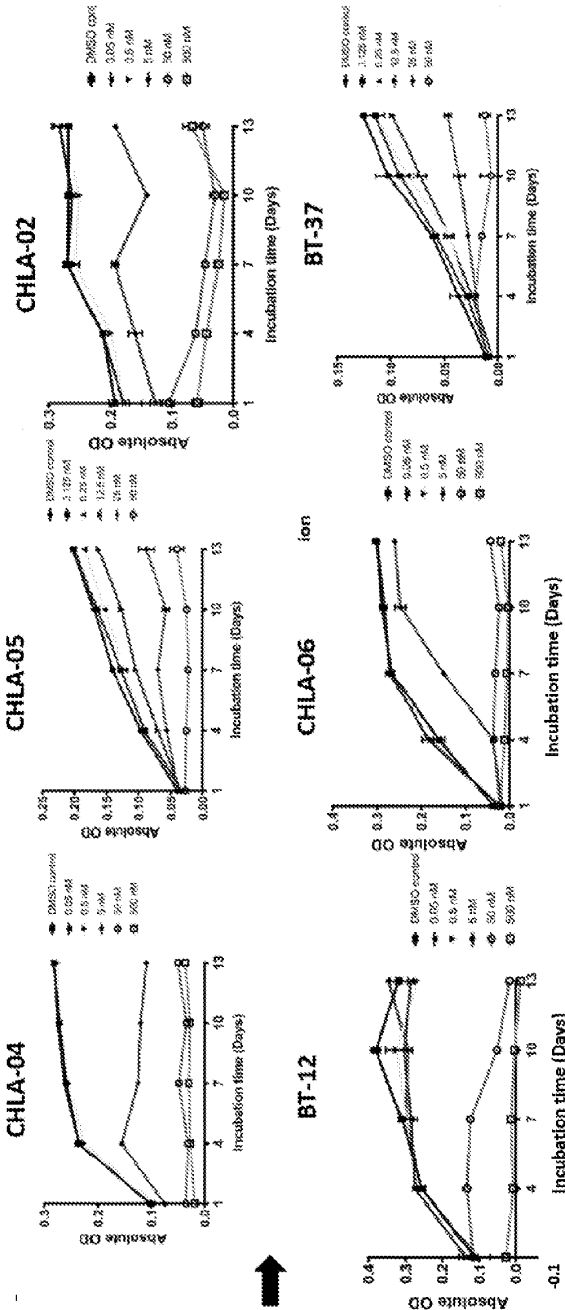


FIG. 5B

MELK inhibitor (OTSSP167) induces cell death of ATRT cells

CHLA-02

BT-37

DMSOOTSSP167DMSOOTSSP167

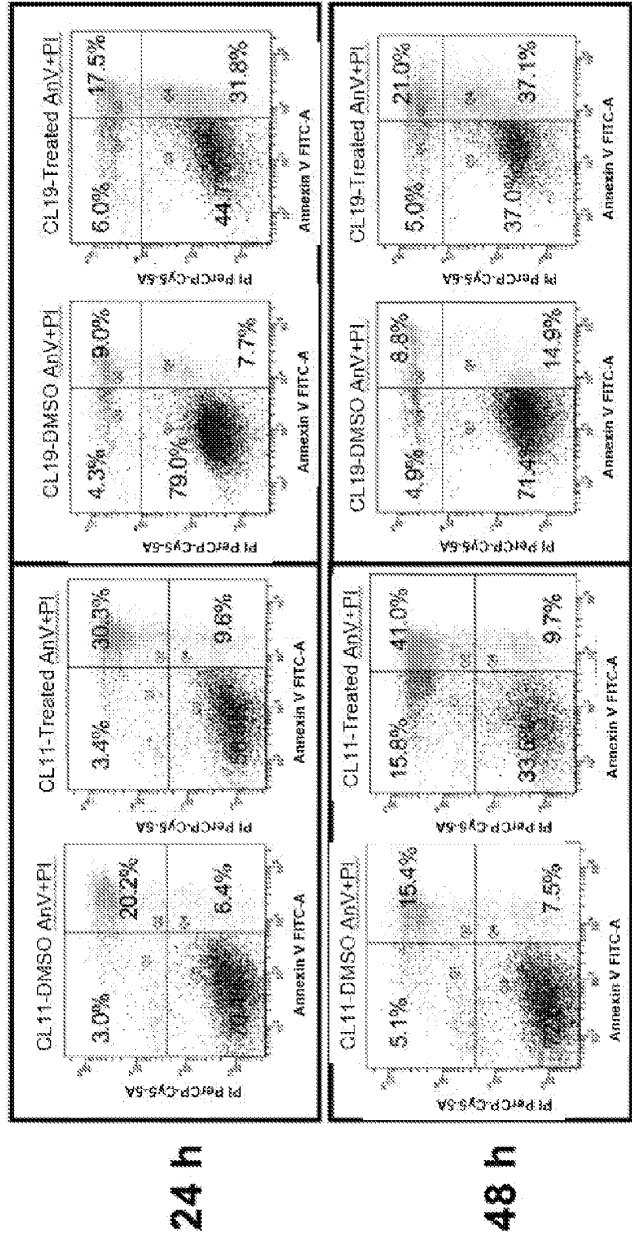


FIG. 5C (continued)



MELK inhibitor (OTSSP167) induces cell death of ATRT cells

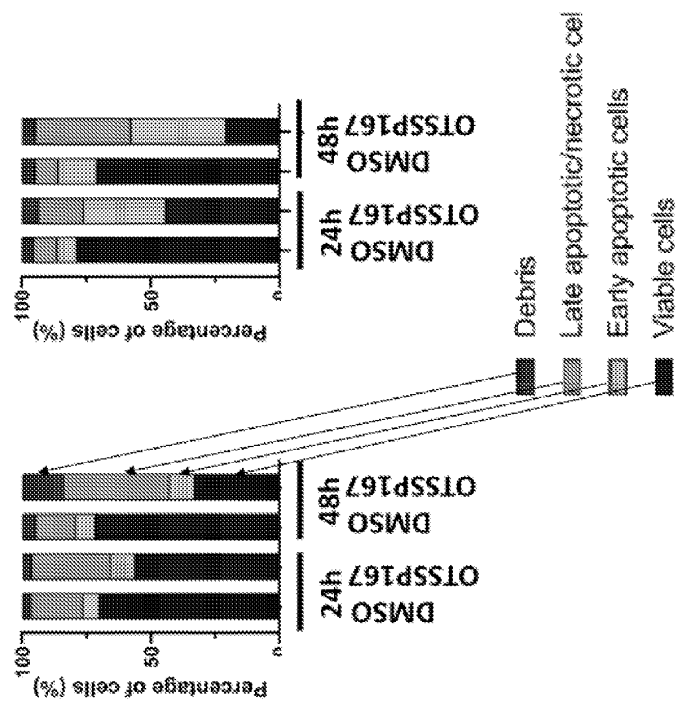


FIG. 5C

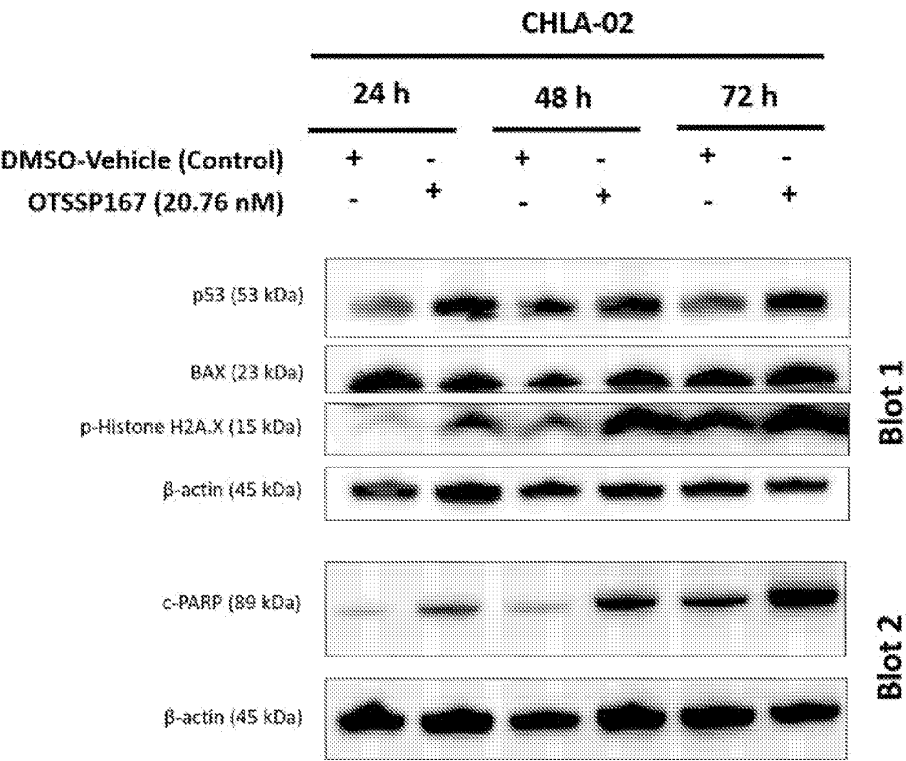


FIG. 5D (continued)

substitute sheet rule 26

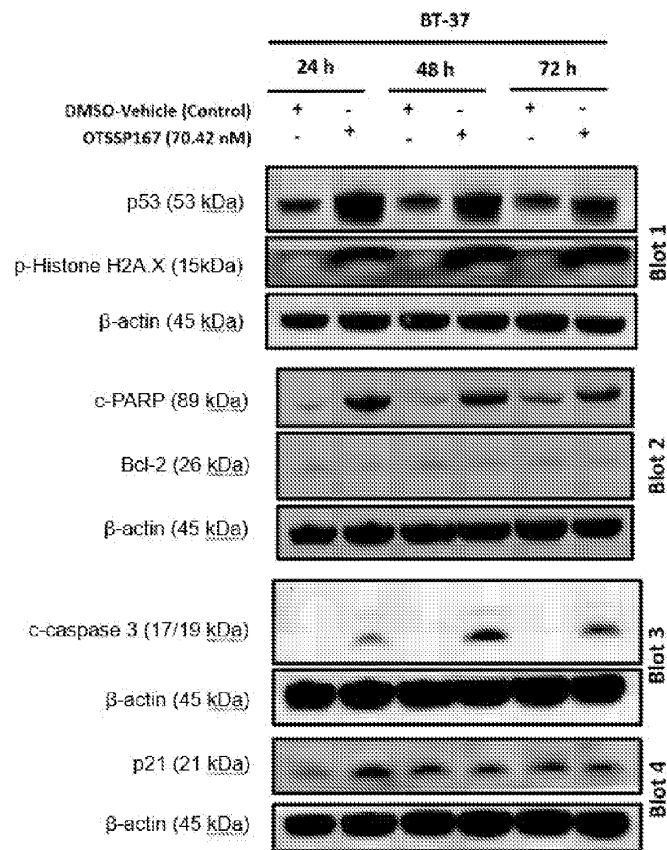


FIG. 5D

A protective niche against initial drug insults to tumor cells

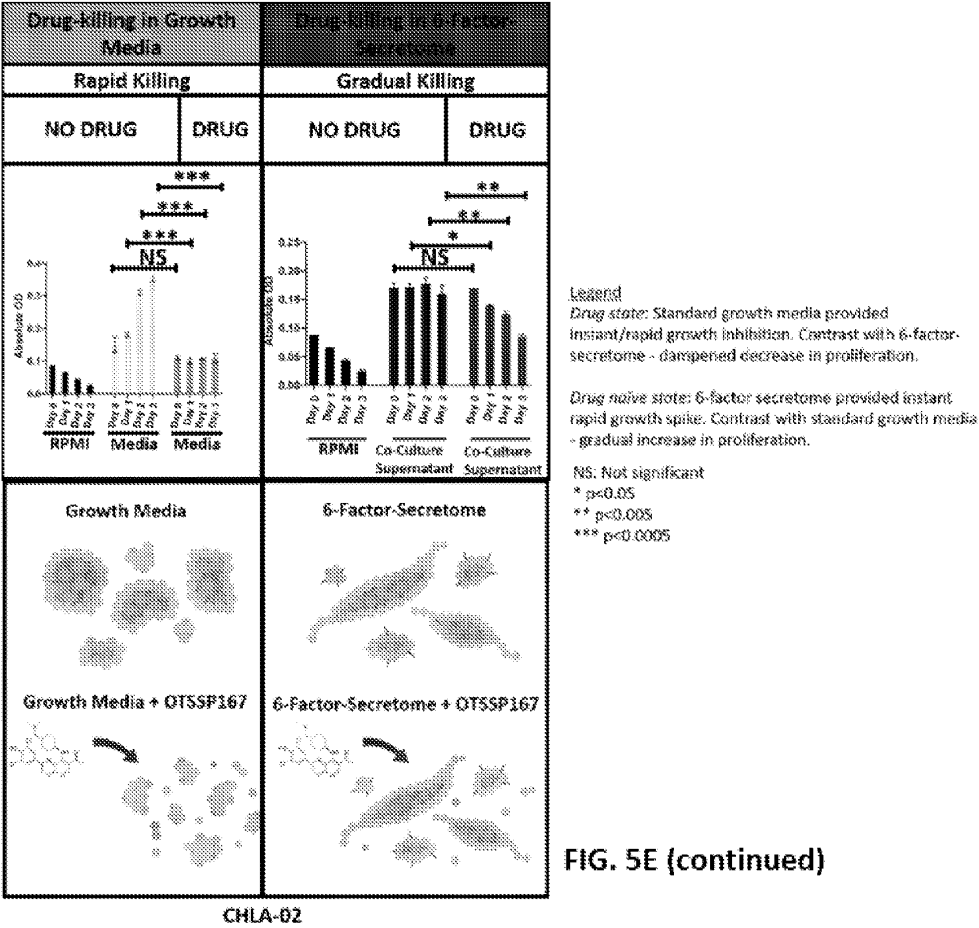


FIG. 5E (continued)

Dampened drug response in secretome environment

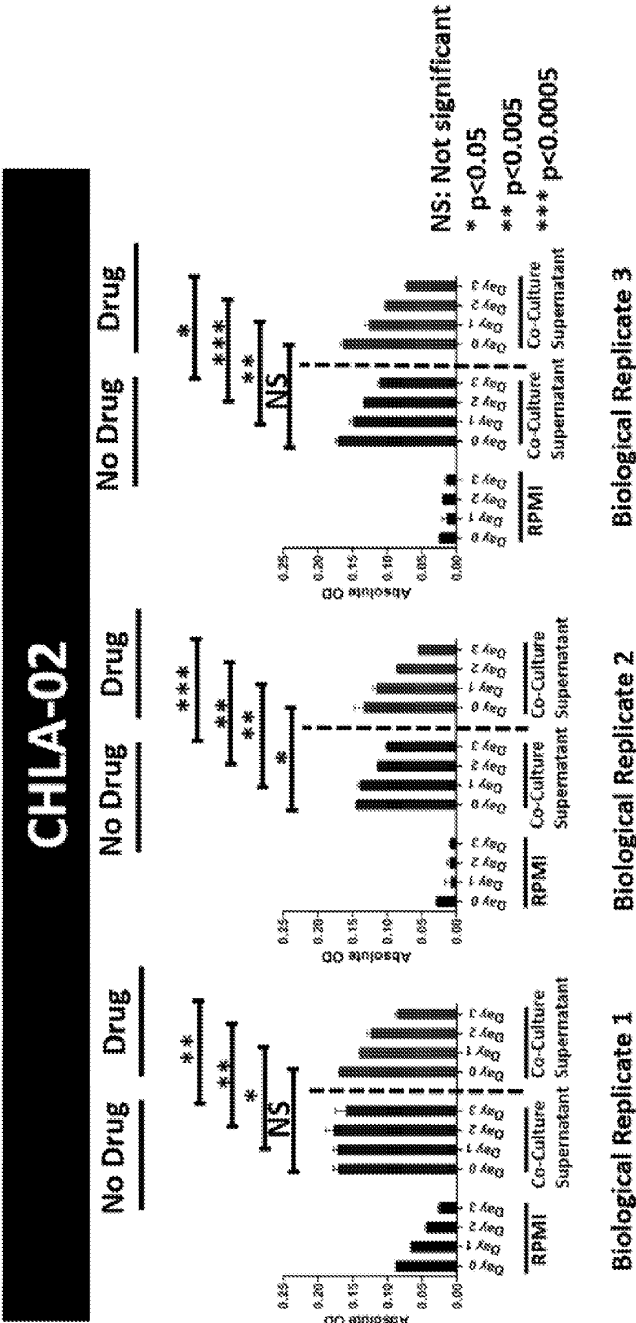


FIG. 5E (continued)



Rapid efficacious drug response in standard growth media

CHLA-02

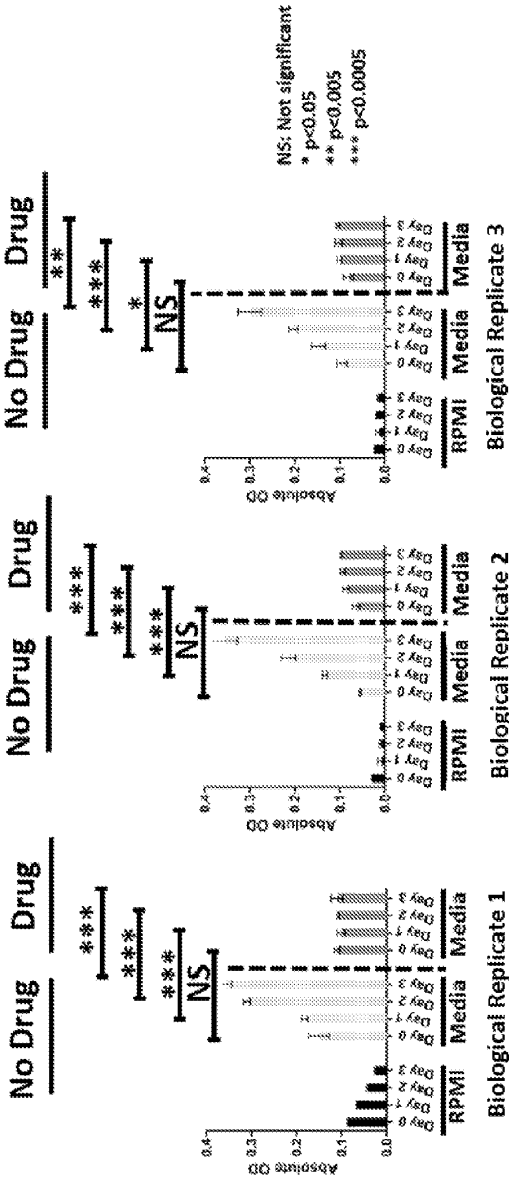


FIG. 5E (continued)

Rapid efficacious drug response in standard growth media

BT-37

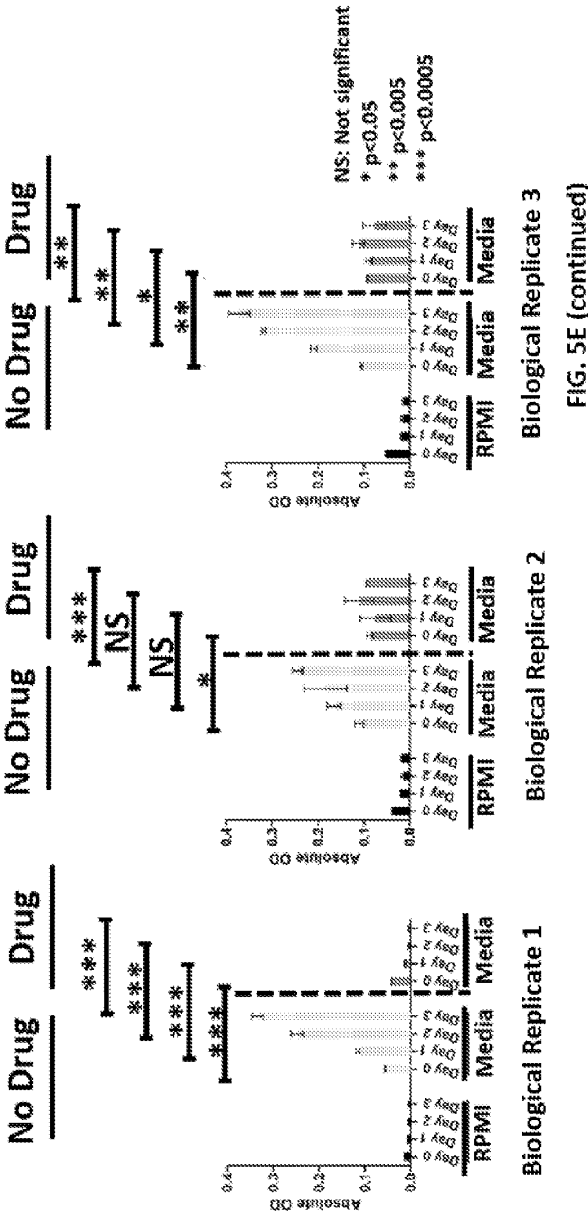


FIG. 5E (continued)



Efficacy of drug is decreased in secretome, compared to standard growth media

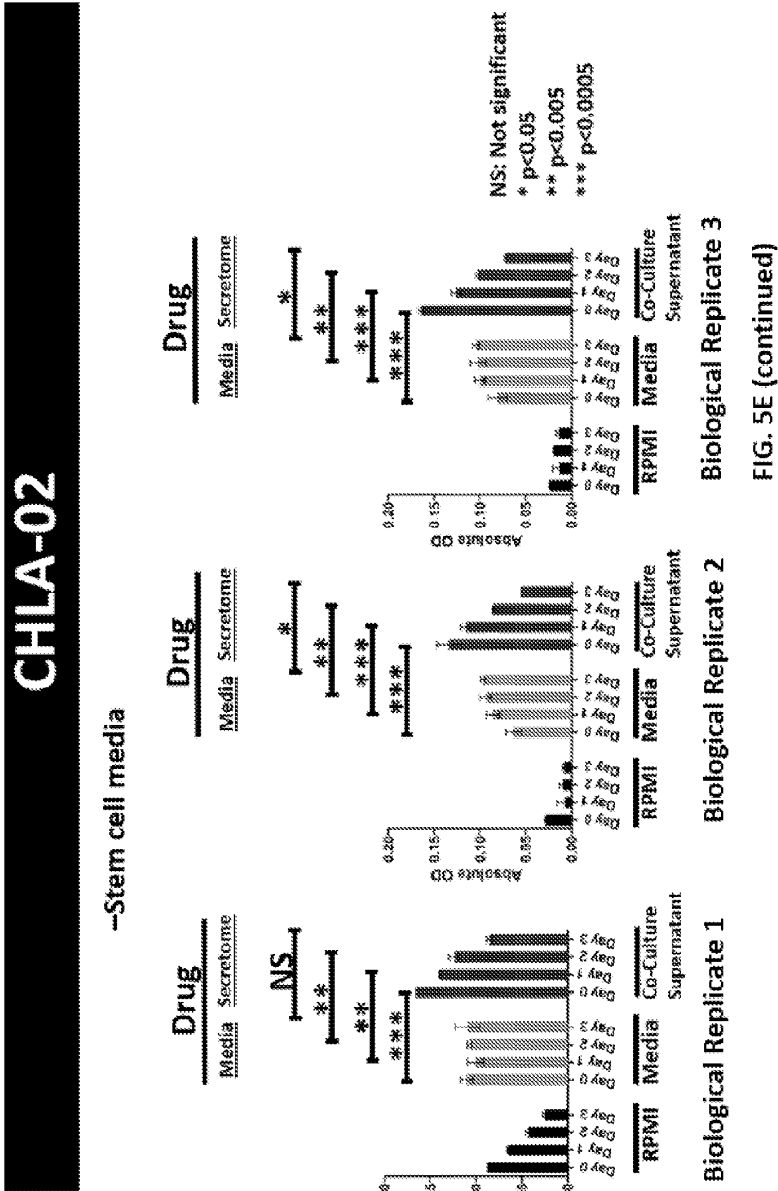
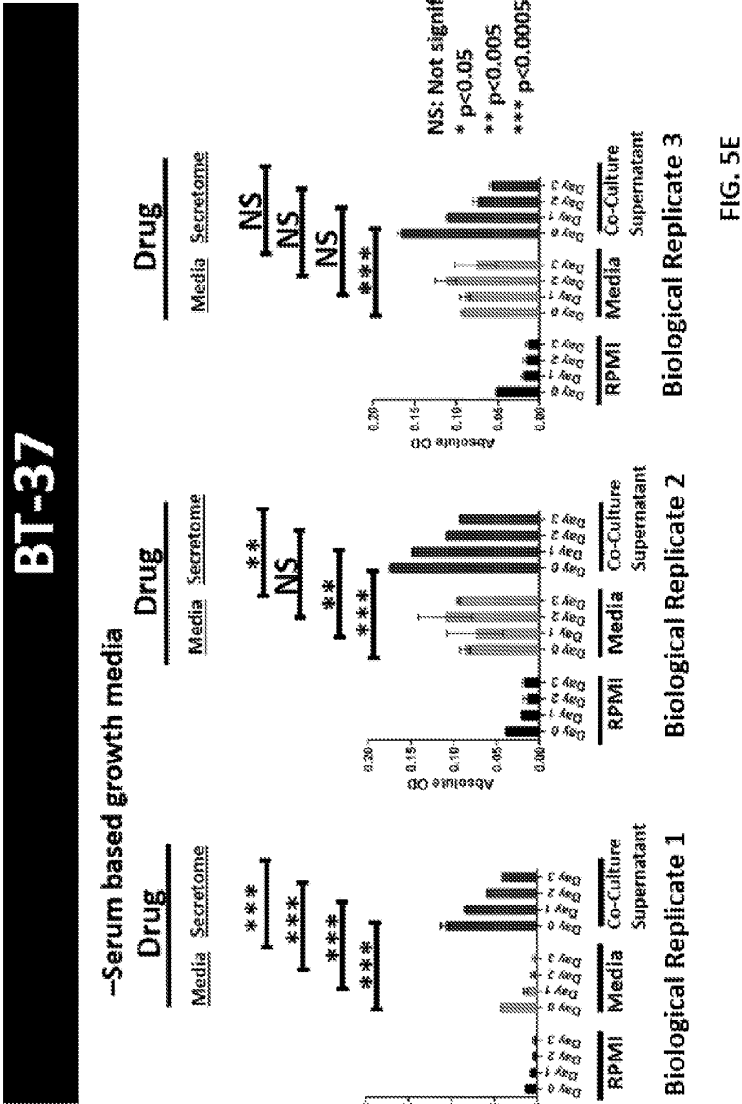


FIG. 5E (continued)

Efficacy of drug is decreased in secretome, compared to standard growth media



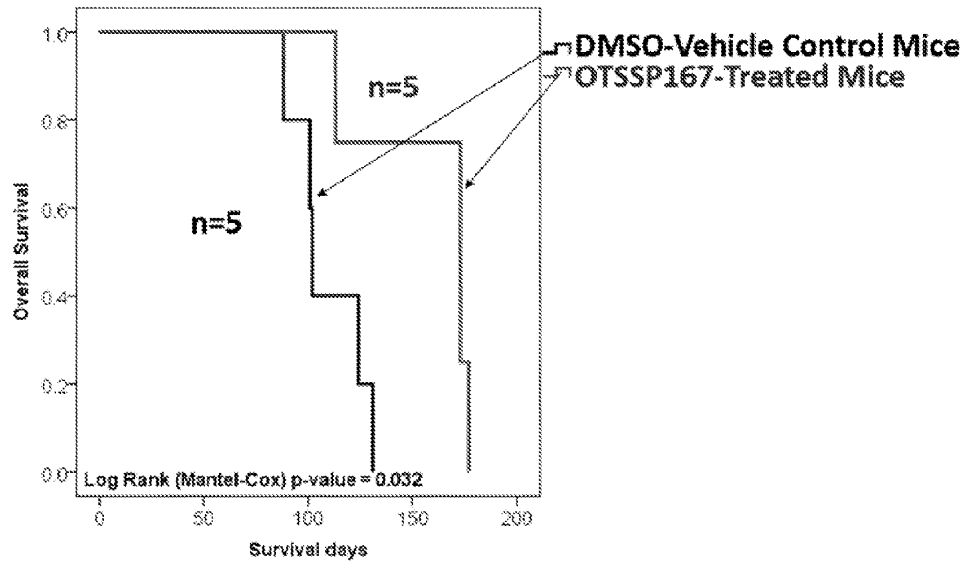
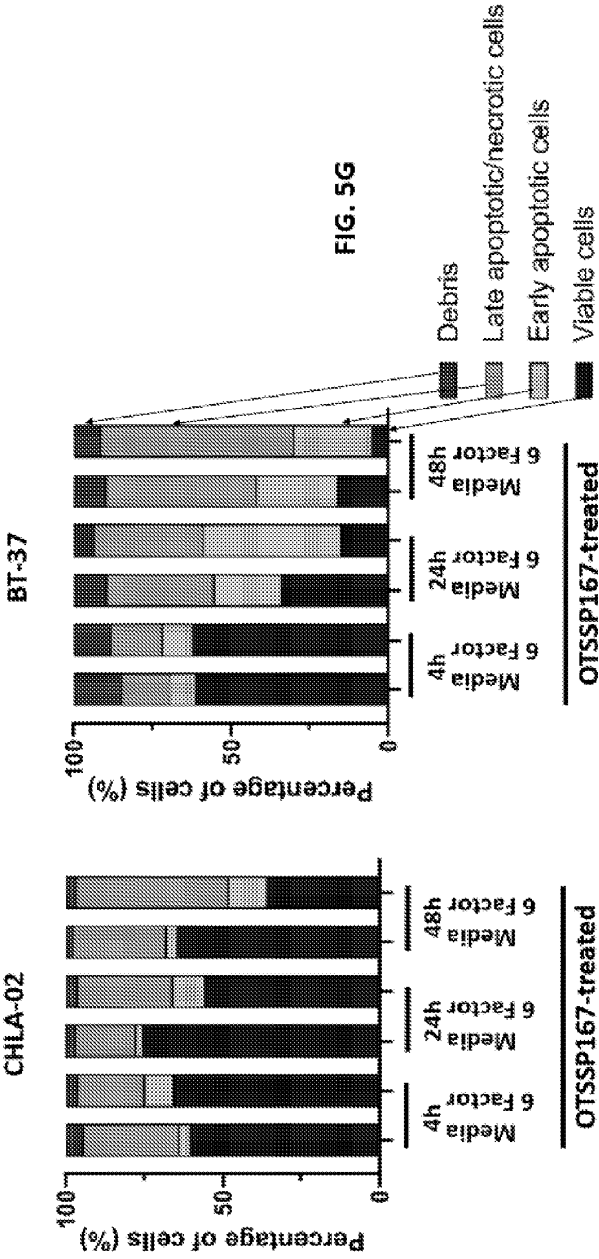


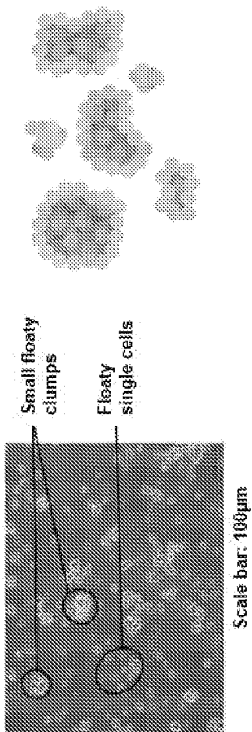
FIG. 5F



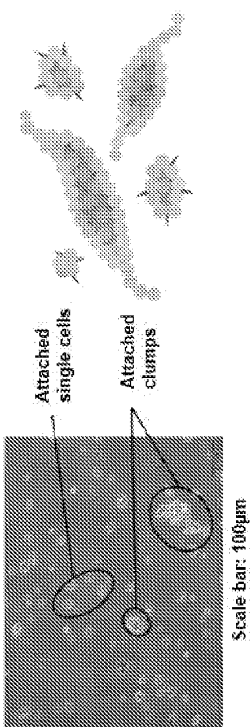
CHLA-02

At 4 hours -- OTSSP167

Standard Media

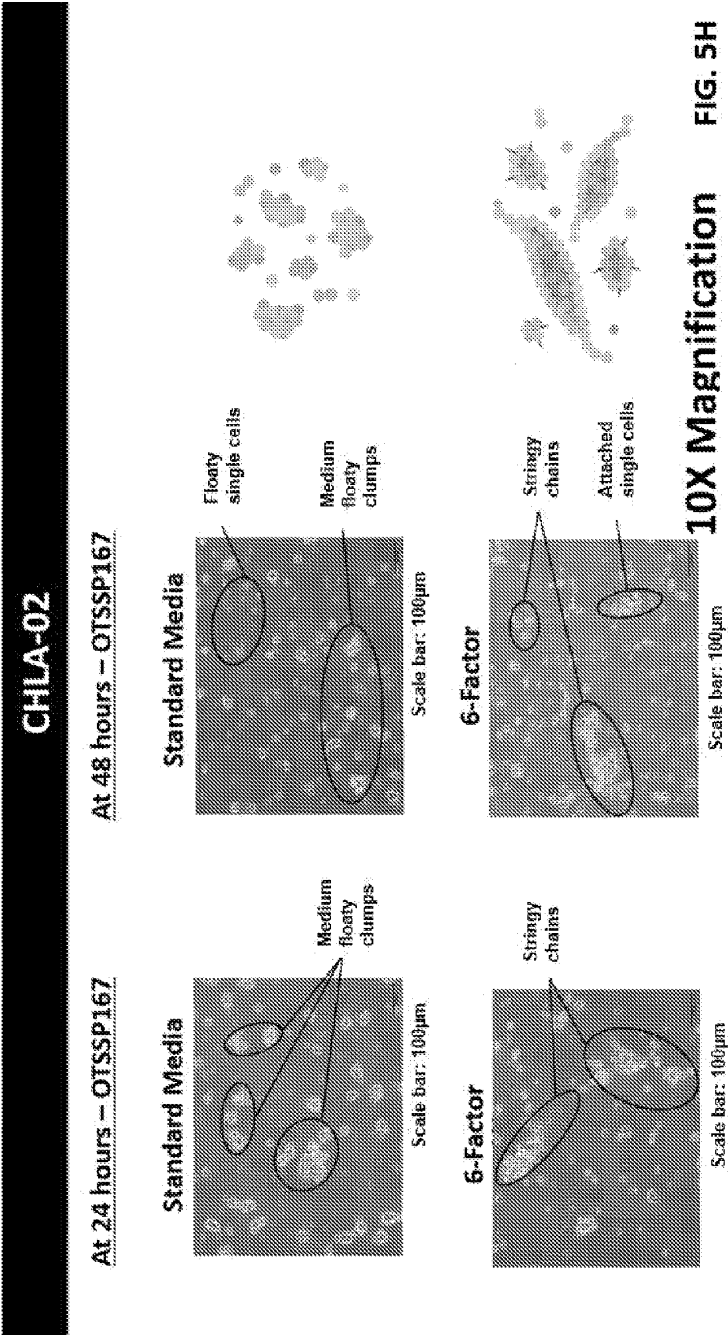


6-Factor

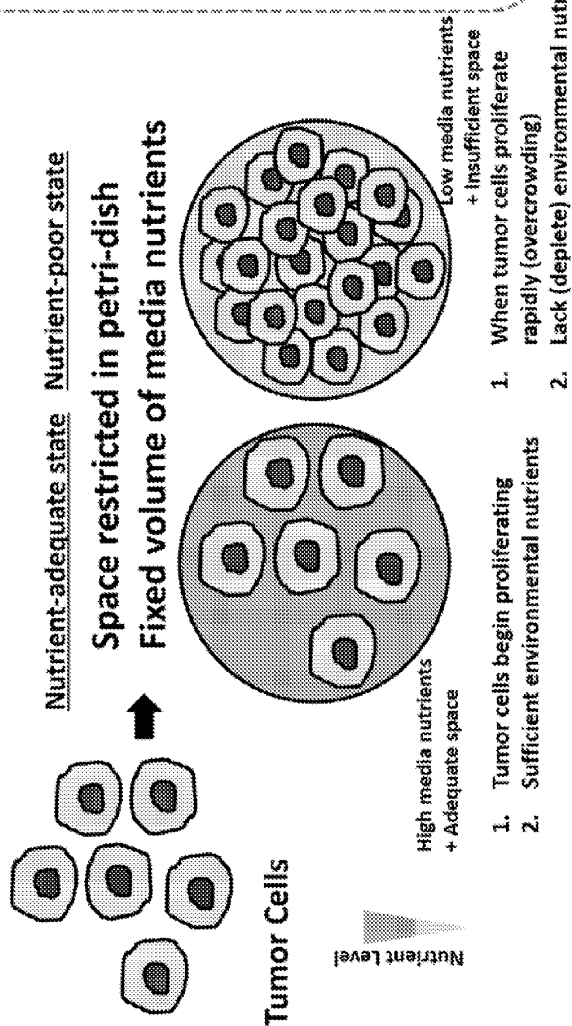


10x magnification

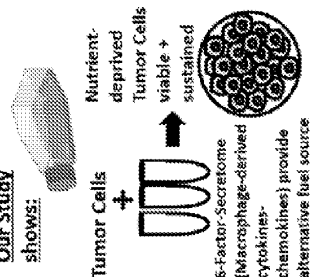
FIG. 5H (continued)



## Reprogramming of cancer cells during nutrient stress



**Our Study shows:**



| Molecular Subtypes of ATRT:<br>Atypical Teratoid Rhabdoid Tumor |                                                                                   |                                                   |
|-----------------------------------------------------------------|-----------------------------------------------------------------------------------|---------------------------------------------------|
| <b>MYC-Subtype</b>                                              |  | E-factor:<br>Secreted tumor<br>inhibitor<br>SIT-1 |
| <b>SHH-Subtype</b>                                              |                                                                                   | E-factor:<br>secretagogue<br>SCW                  |
| <b>TYR-Subtype</b>                                              |  | E-factor:<br>Secretagogue<br>receptor<br>TYR      |

**FIG. 6 (continued)**

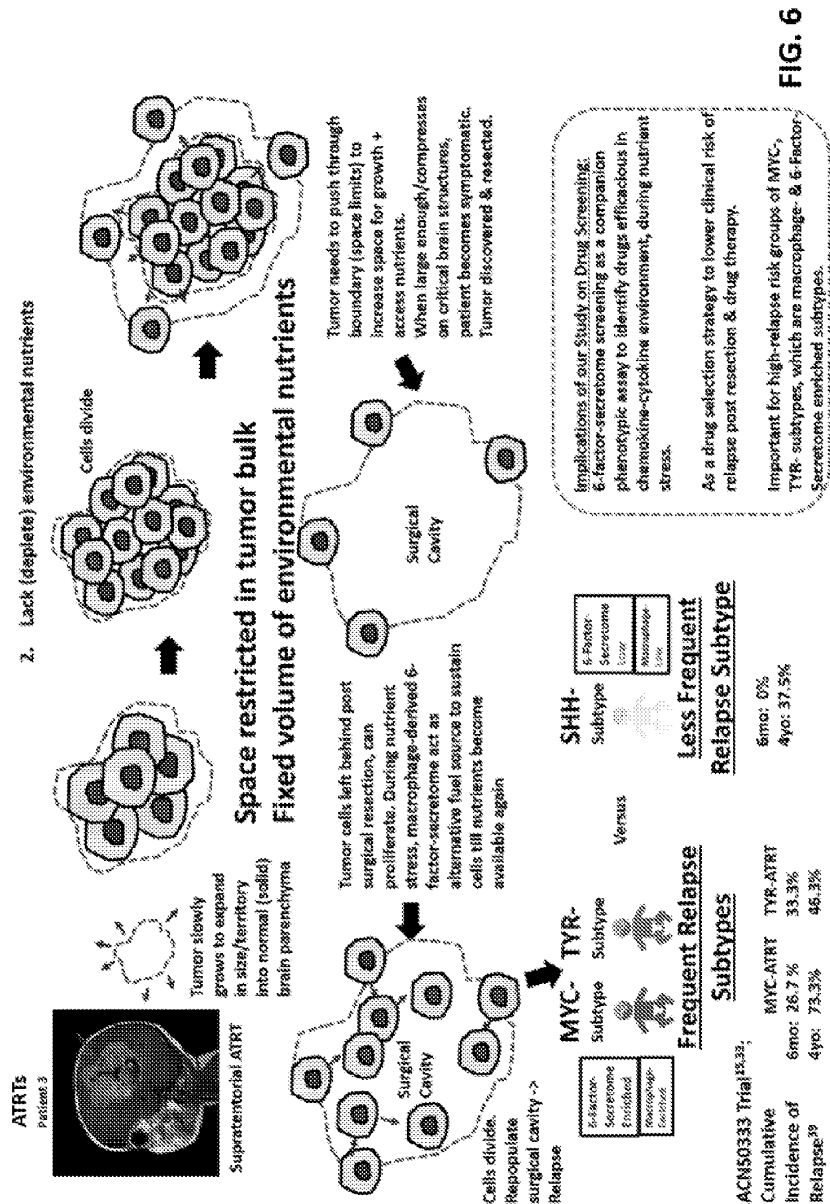


FIG. 6



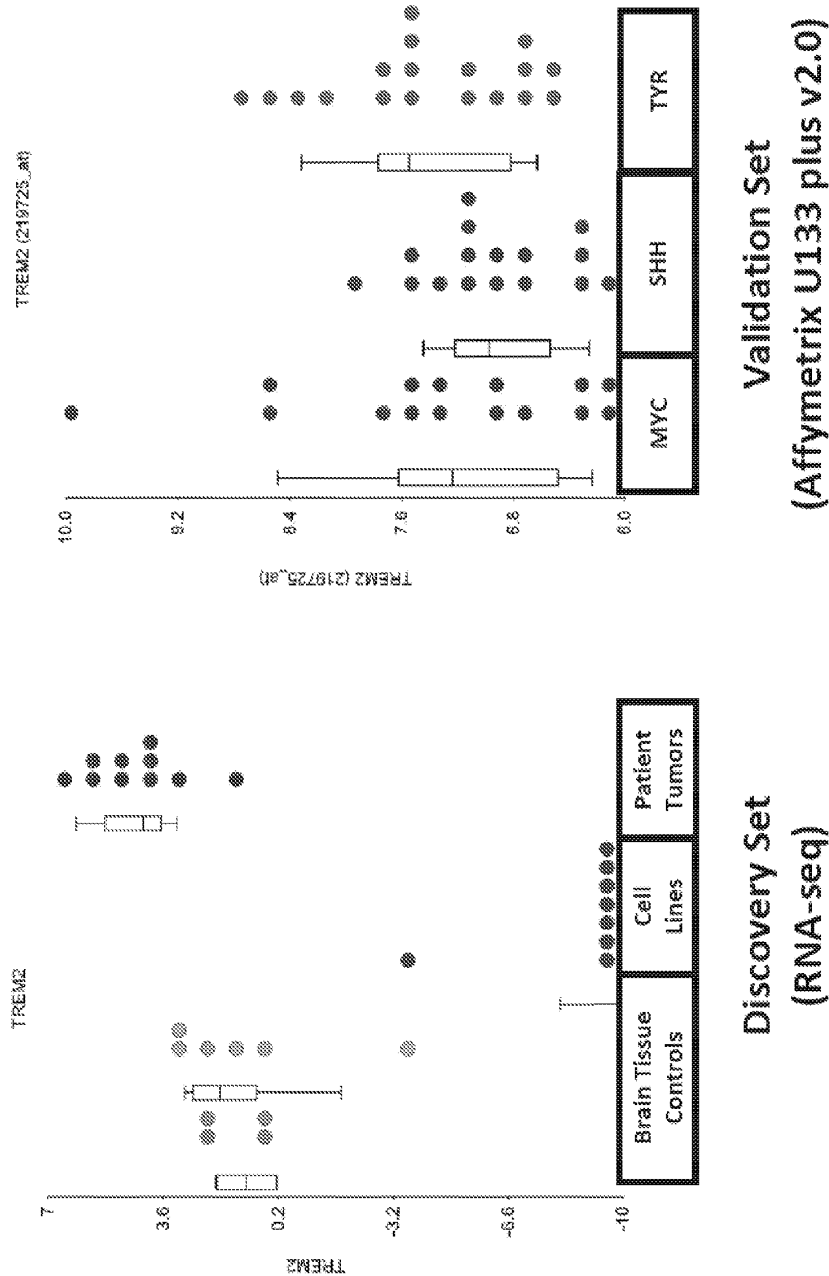


FIG. 7A

FIG. 7B

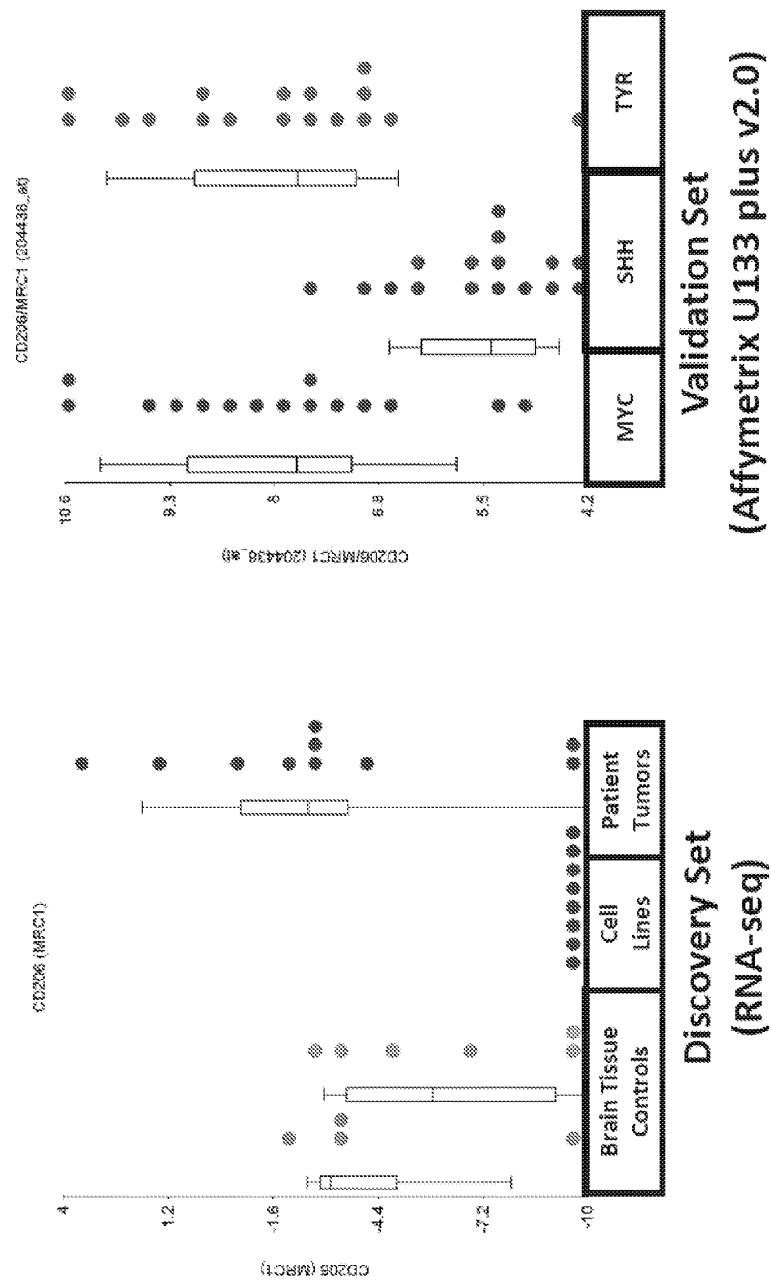
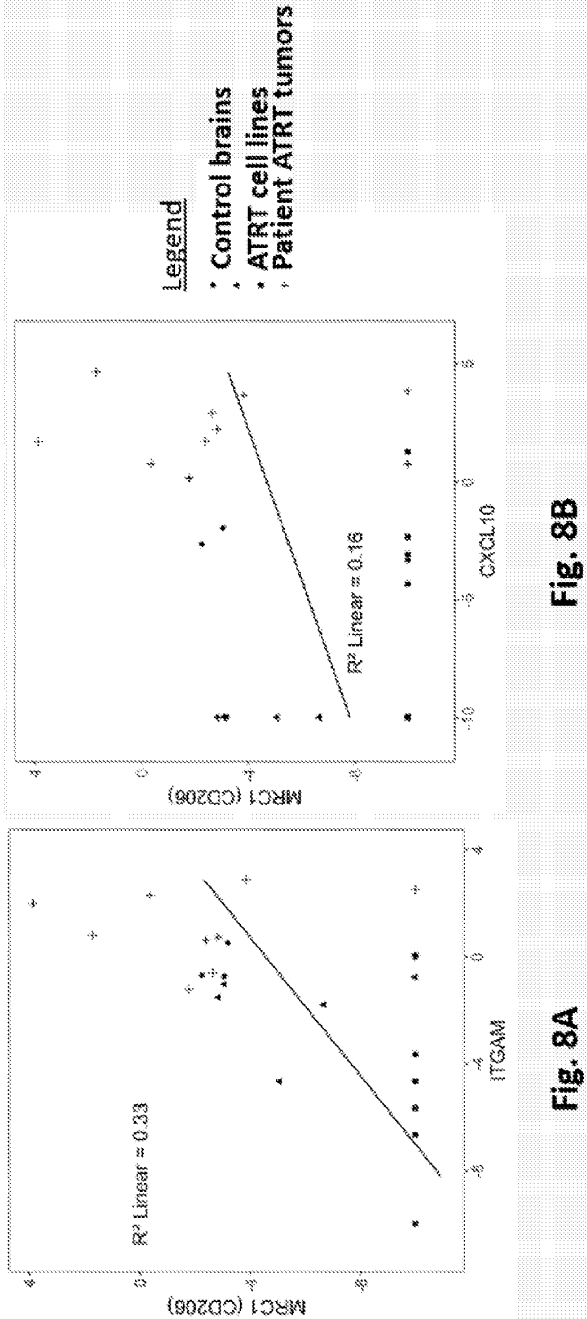
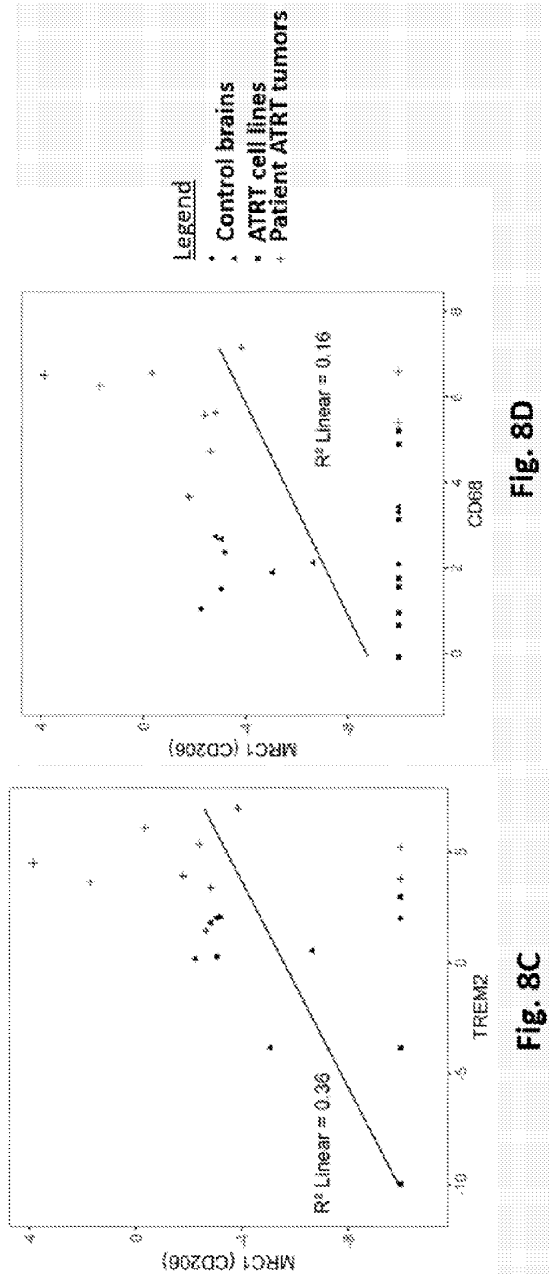


FIG. 7D

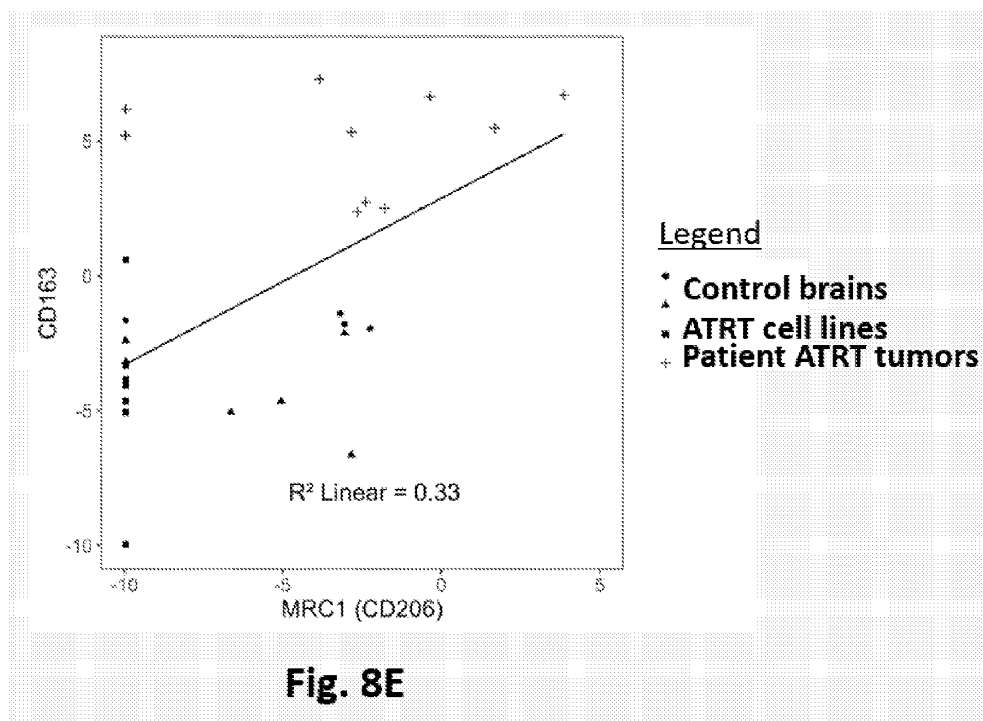
FIG. 7C



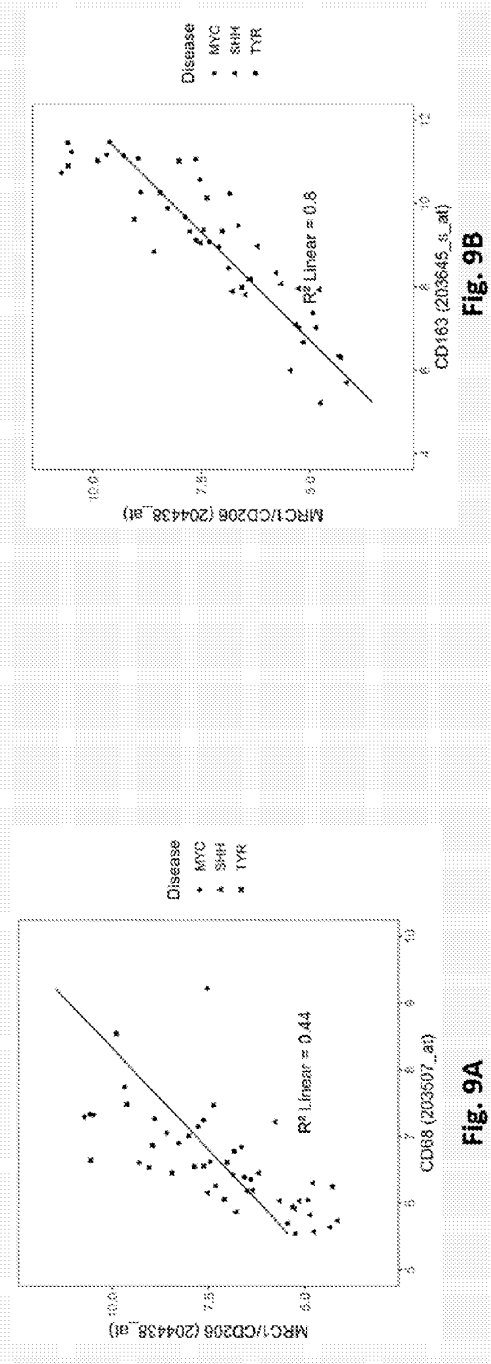
Discovery Set (RNA-Seq)



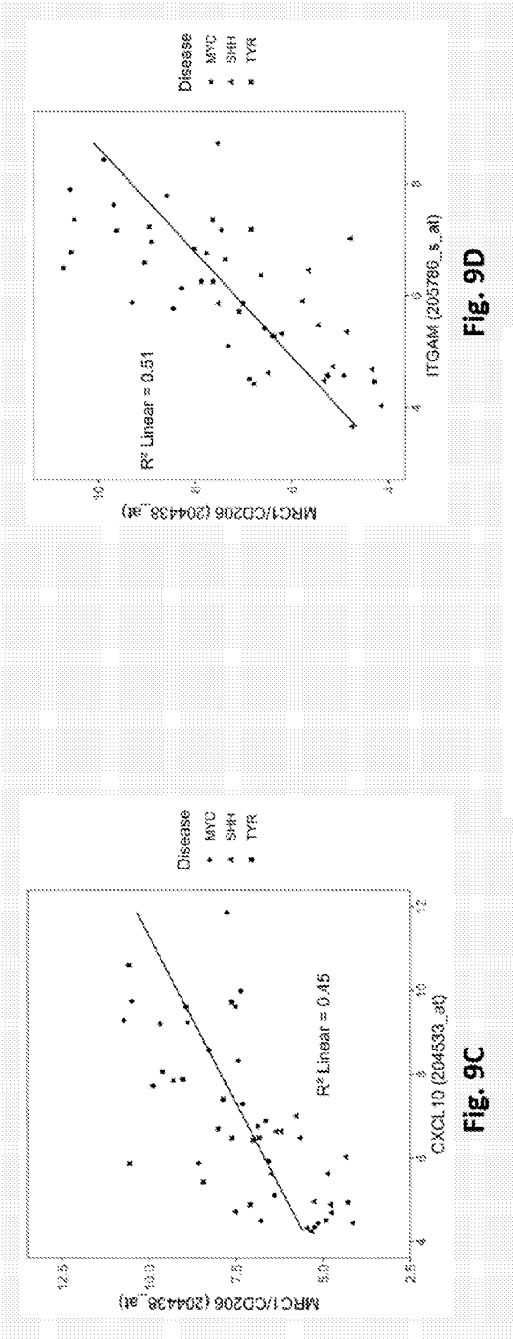
Discovery Set (RNA-Seq)

**Fig. 8E**

Discovery Set  
(RNA-seq)



Validation Set  
(Affymetrix U133 plus 2.0)



Validation Set  
(Affymetrix U133 plus 2.0)

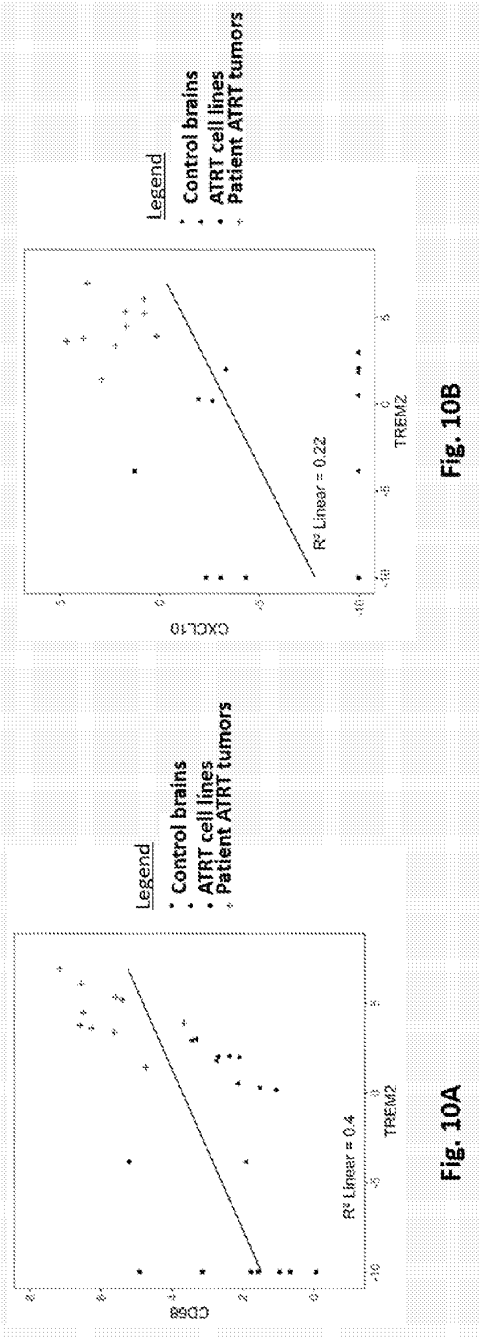
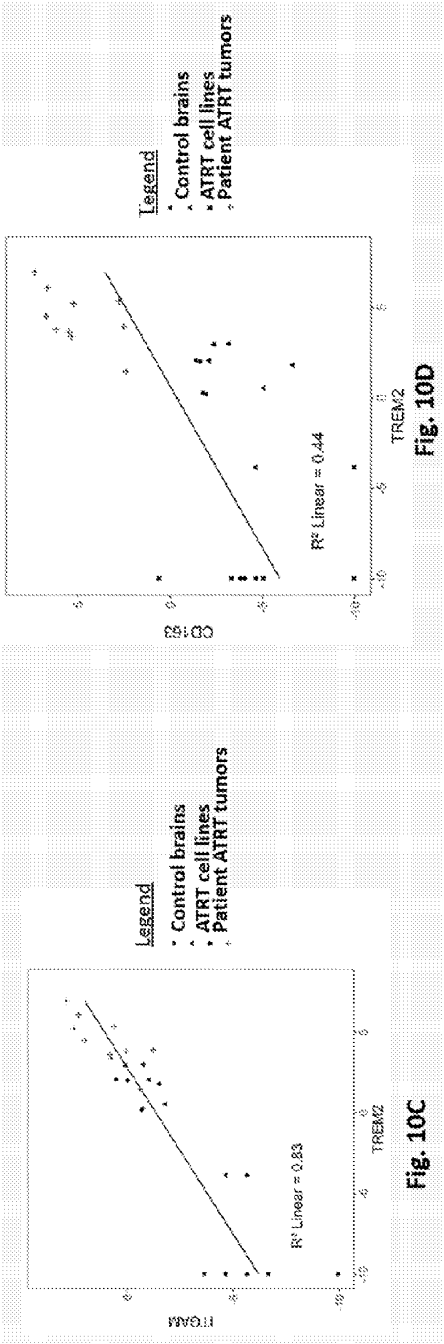


Fig. 10B

Fig. 10A

Discovery Set  
(RNA-seq)





Discovery Set  
(RNA-seq)

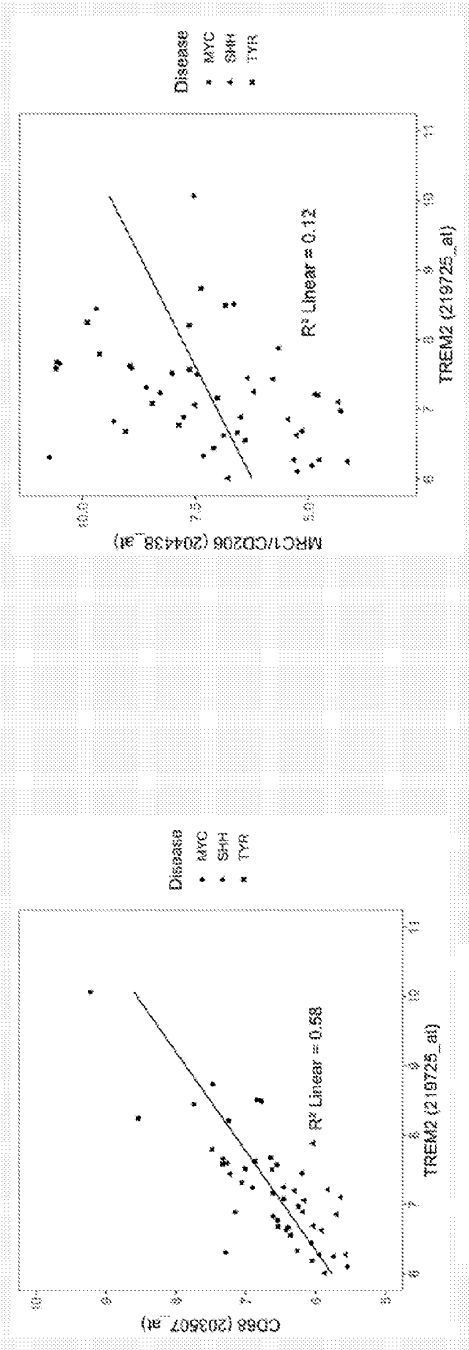
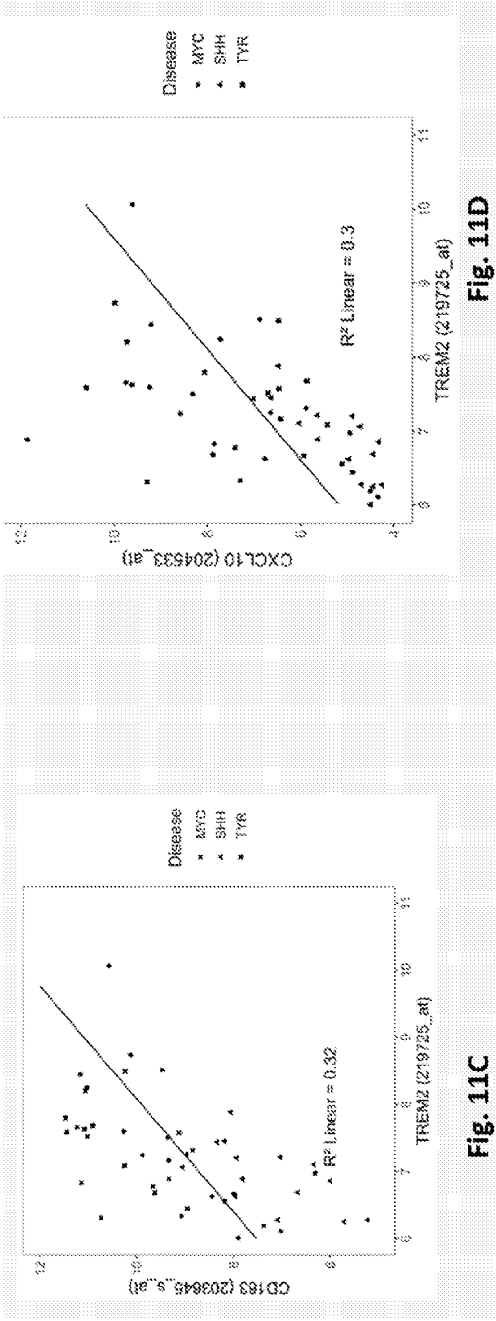


FIG. 11B

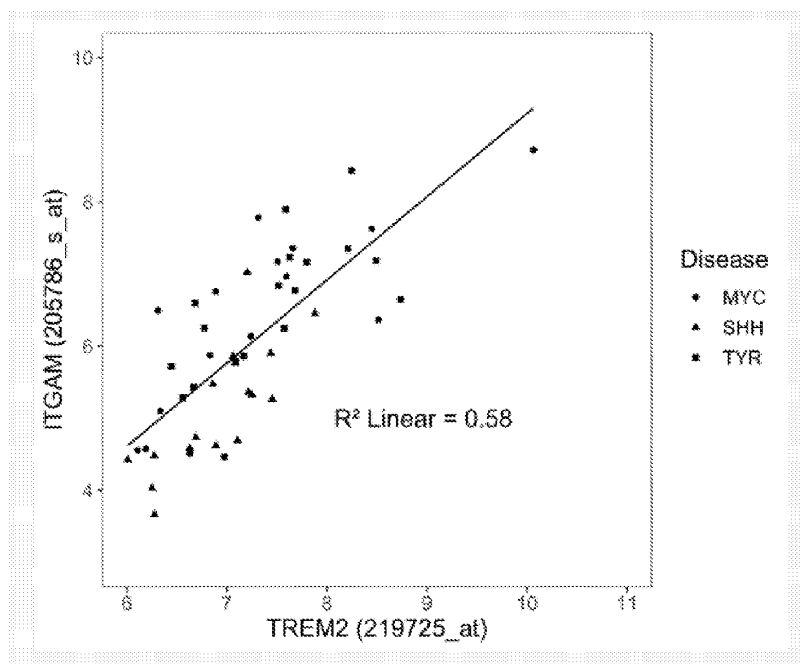
Validation Set

(Affymetrix U133 plus 2.0)

FIG. 11A



Validation Set  
(Affymetrix U133 plus 2.0)

**FIG. 11E**

**Validation Set**  
**(Affymetrix U133 plus 2.0)**

|    |   |
|----|---|
| 12 | 2 |
| 18 | 4 |
| 1  | 3 |

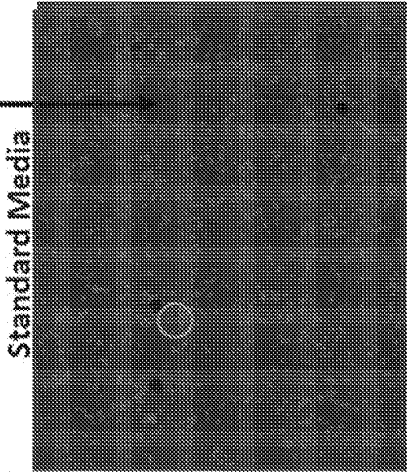
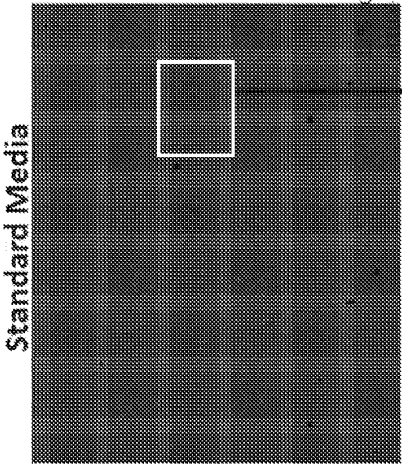
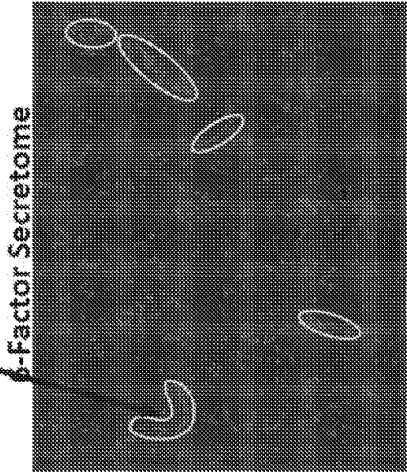
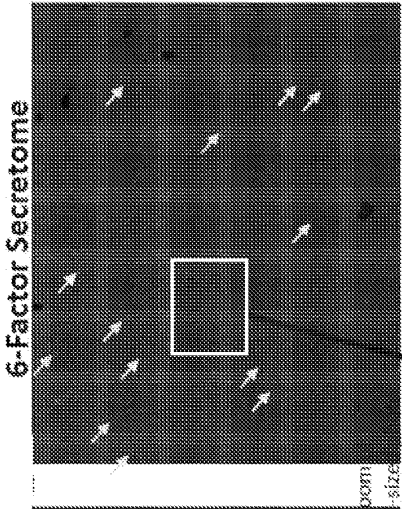


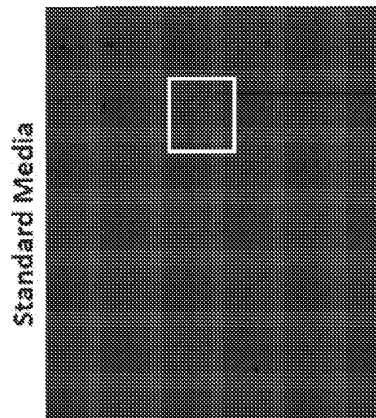
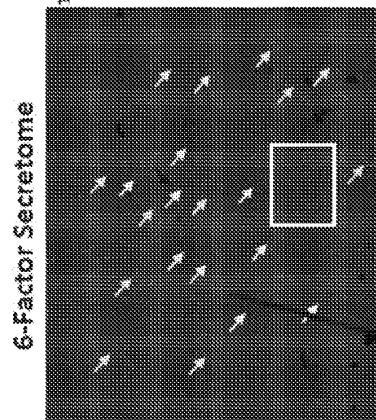
FIG. 12B

FIG. 12D

FIG. 12A

FIG. 12C

|    |   |   |
|----|---|---|
| 18 | 1 | 2 |
| 18 | 3 | 4 |



12% zoom of  
actual sized photo

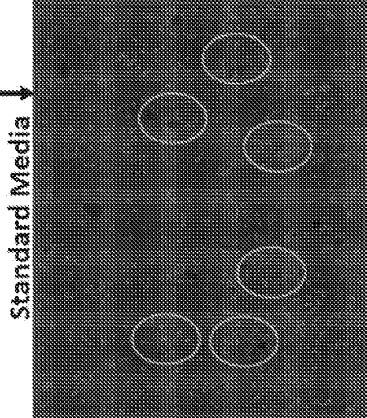
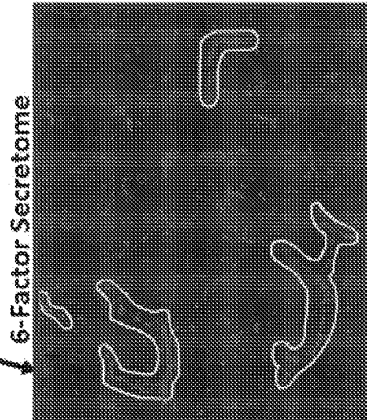
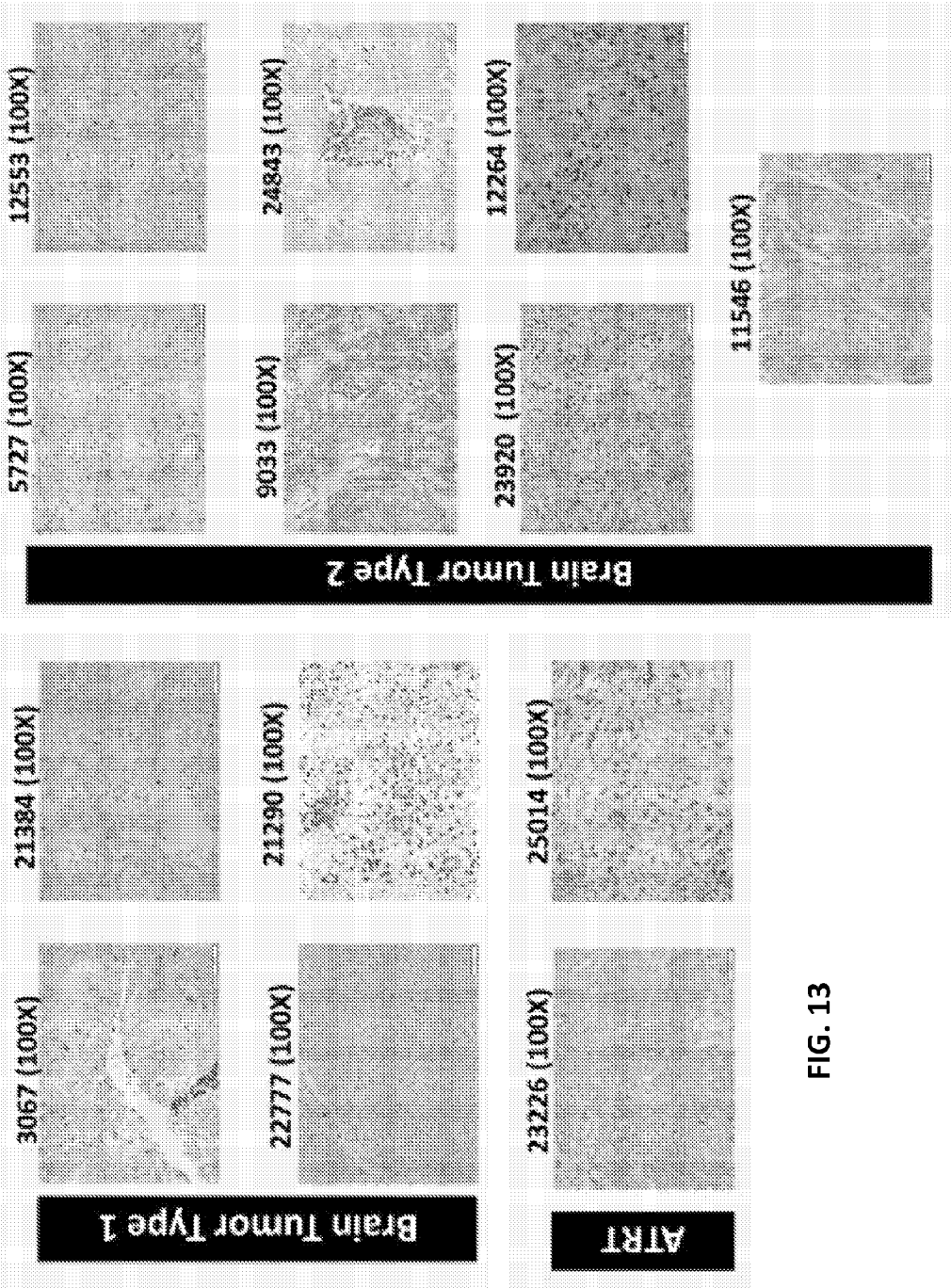


FIG. 12E

FIG. 12F

FIG. 12G

FIG. 12H



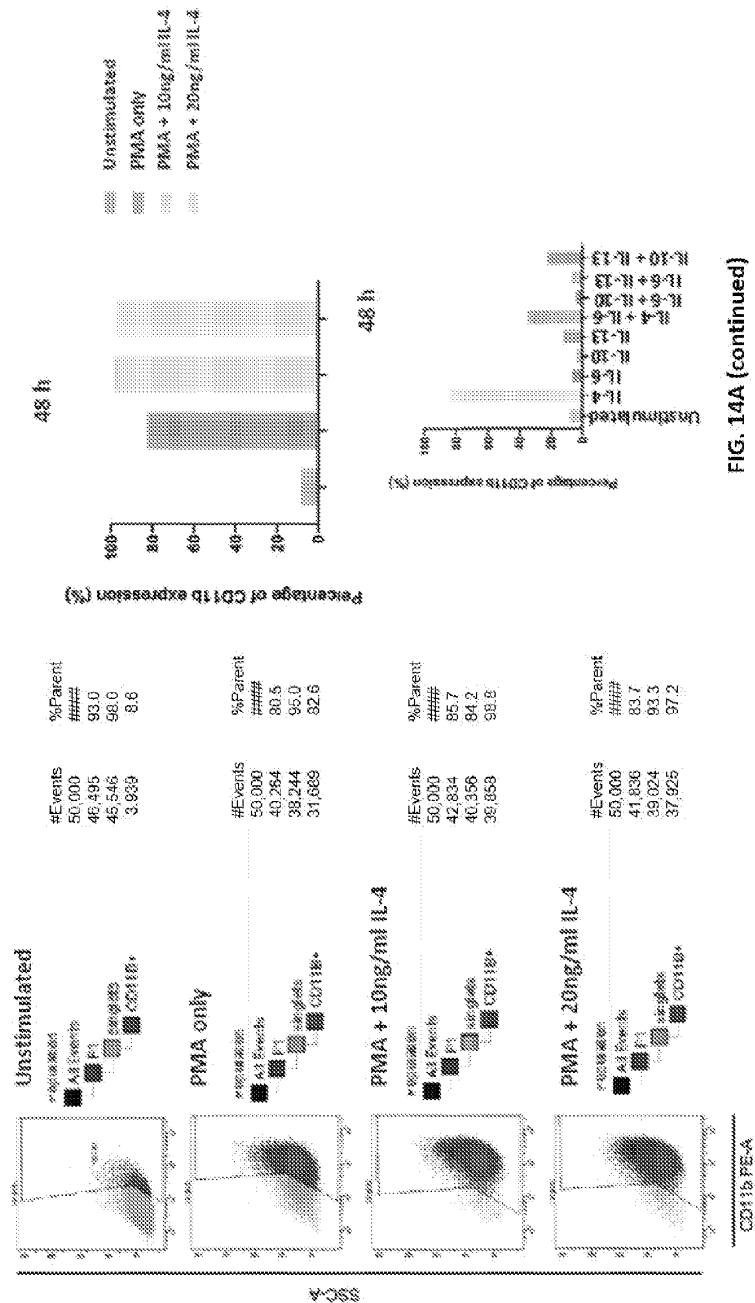


FIG. 14A (continued)



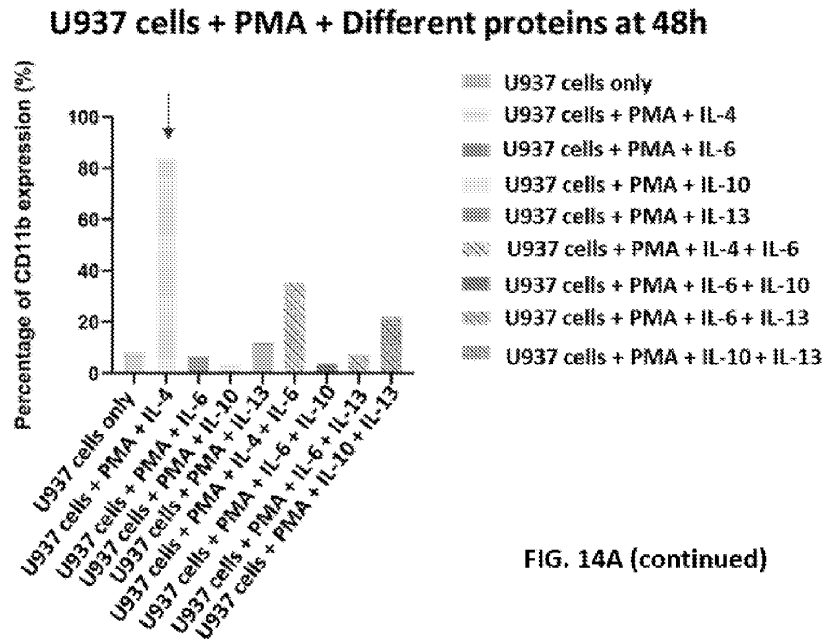


FIG. 14A (continued)

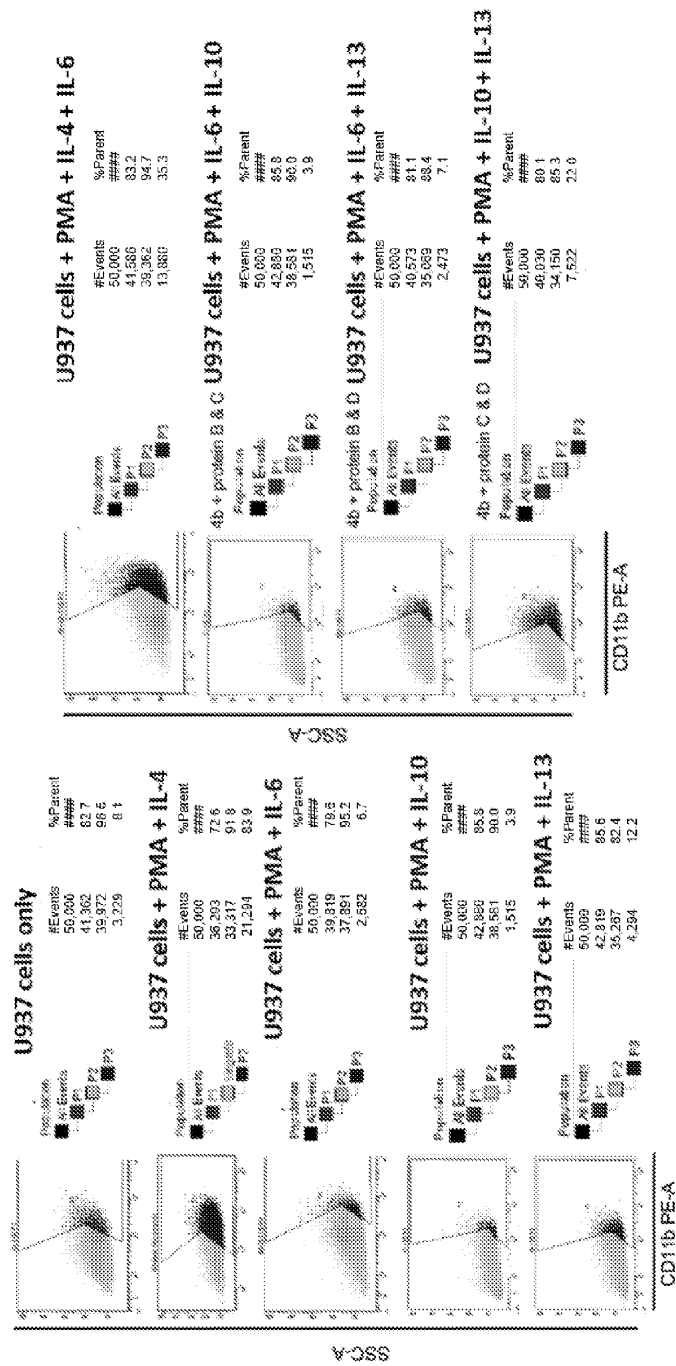


FIG. 14A

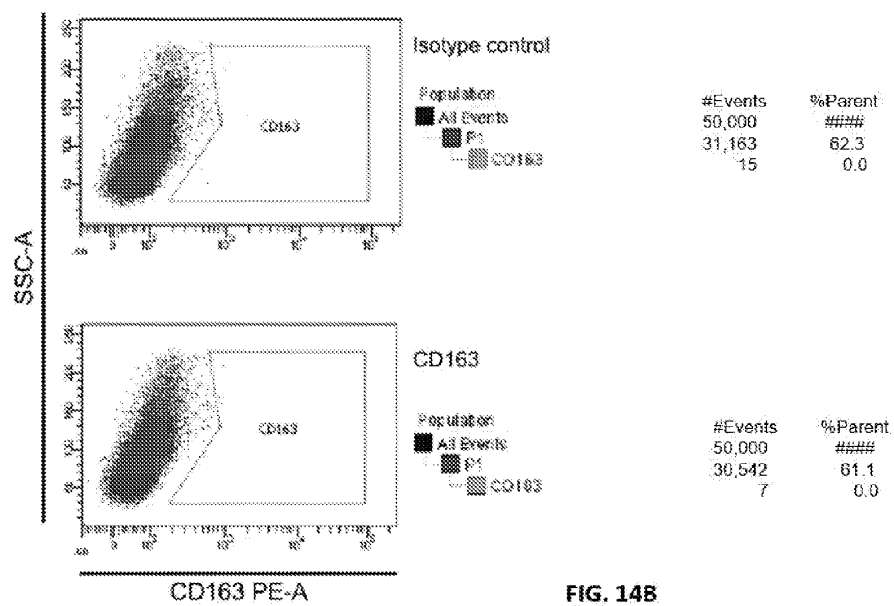


FIG. 14B

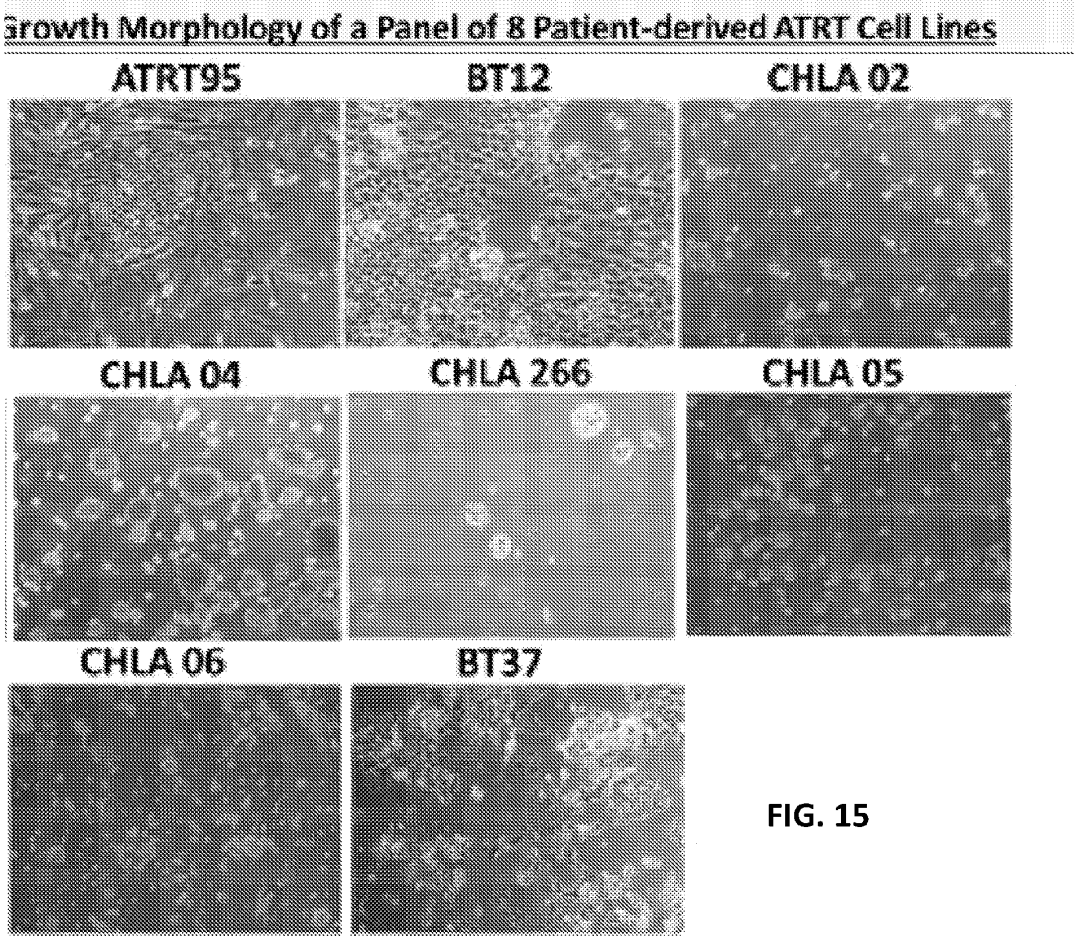


FIG. 15

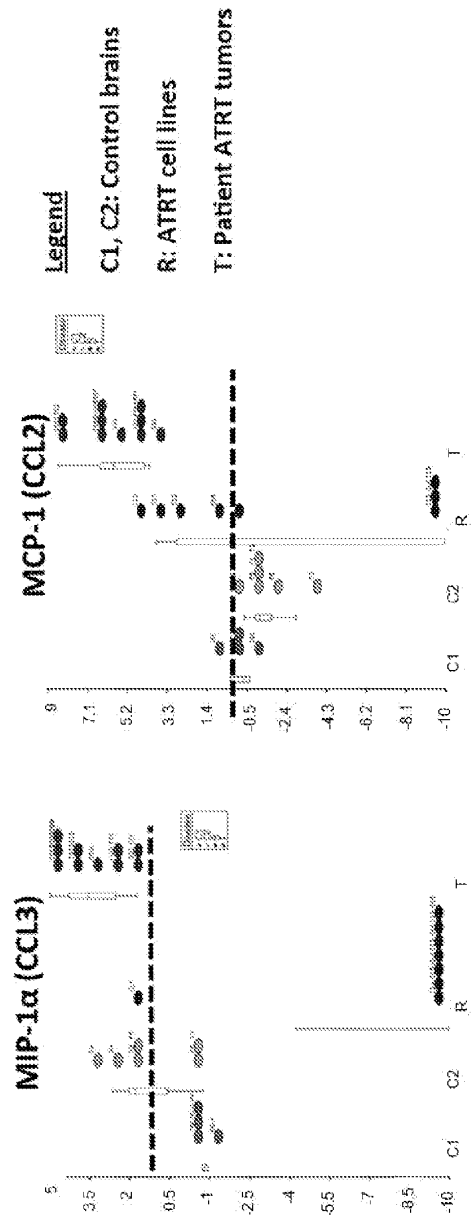


FIG. 16A (continued)

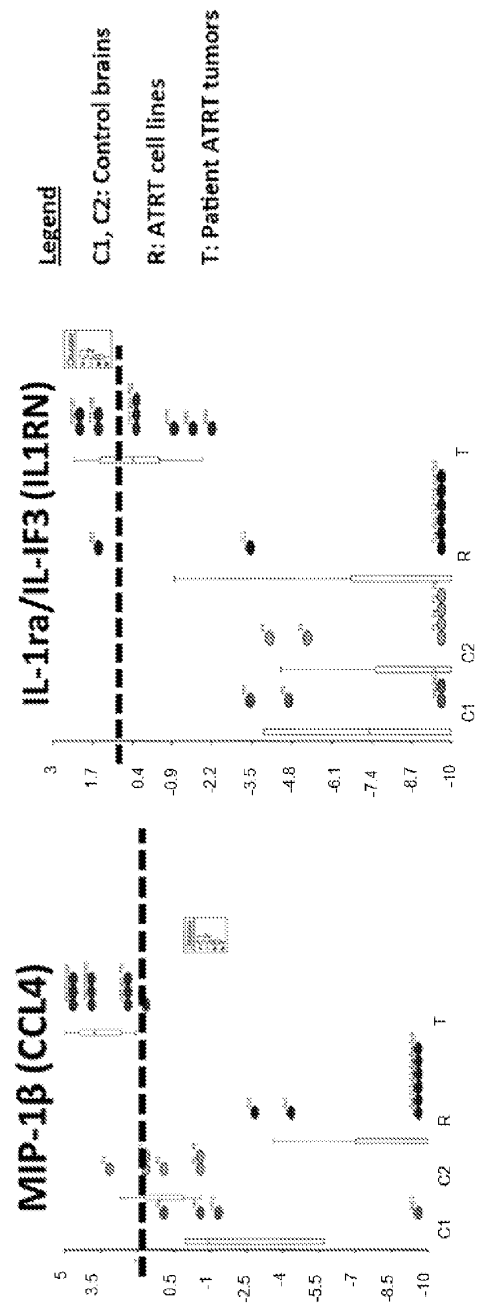


FIG. 16A (continued)

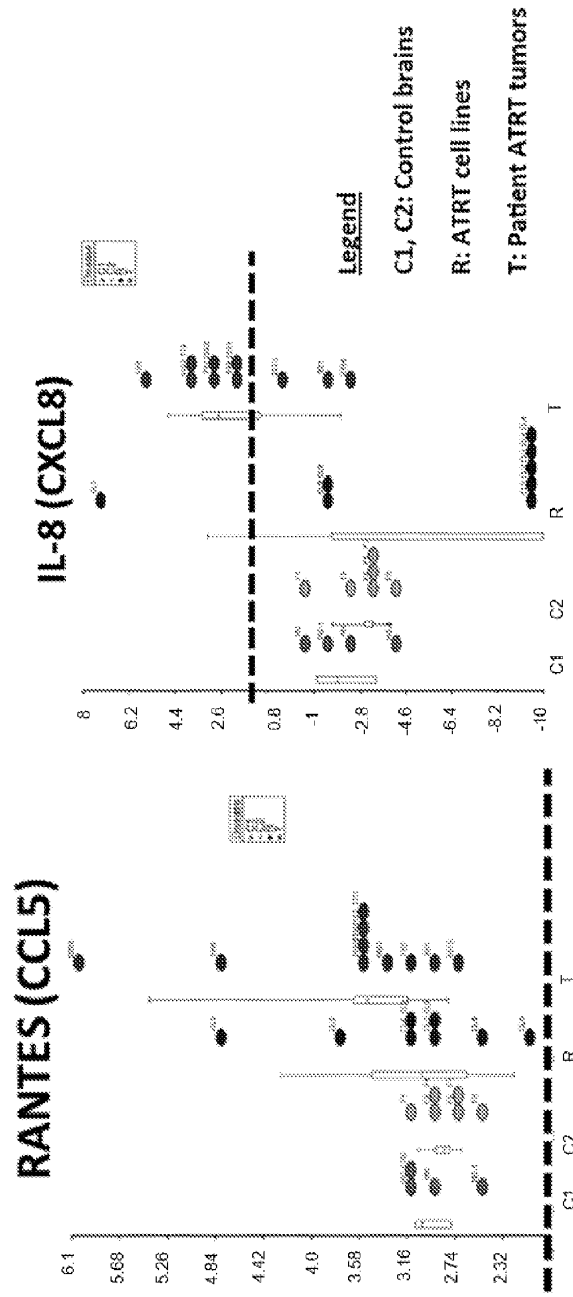


FIG. 16A

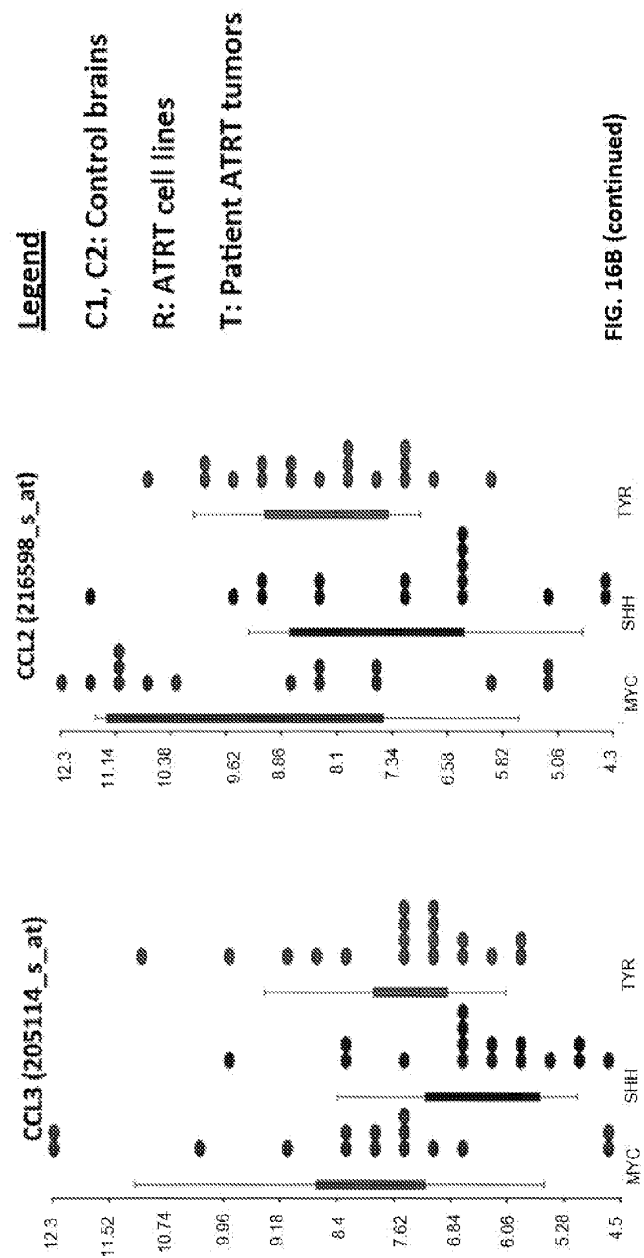


FIG. 16B (continued)



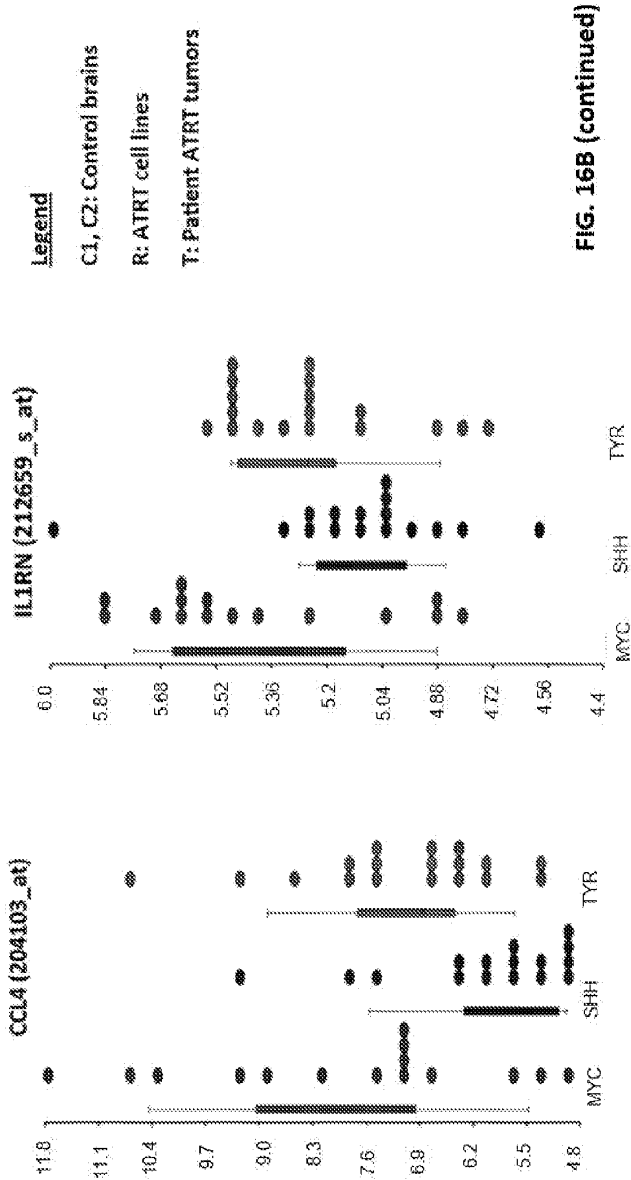


FIG. 16B (continued)

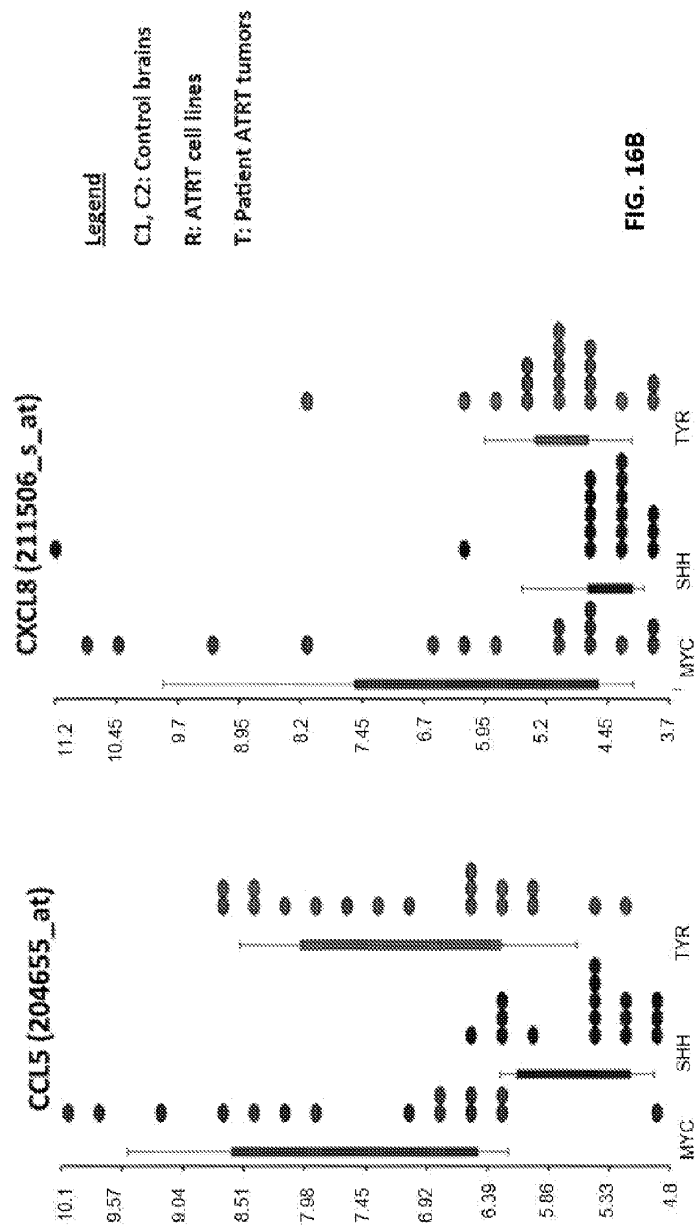


FIG. 16B

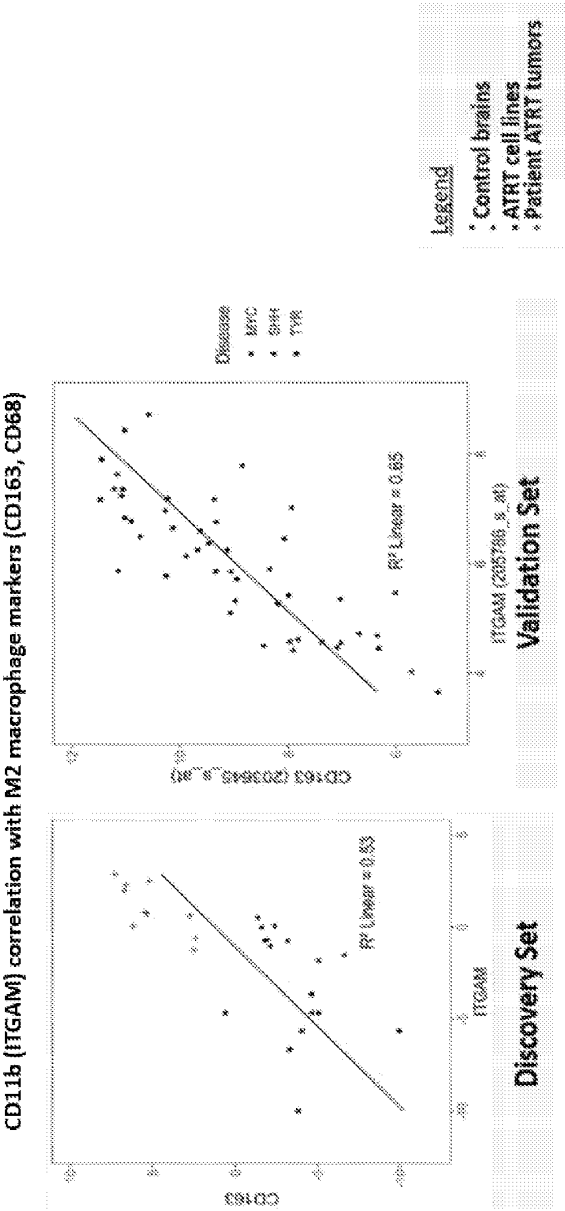


FIG. 17A (continued)

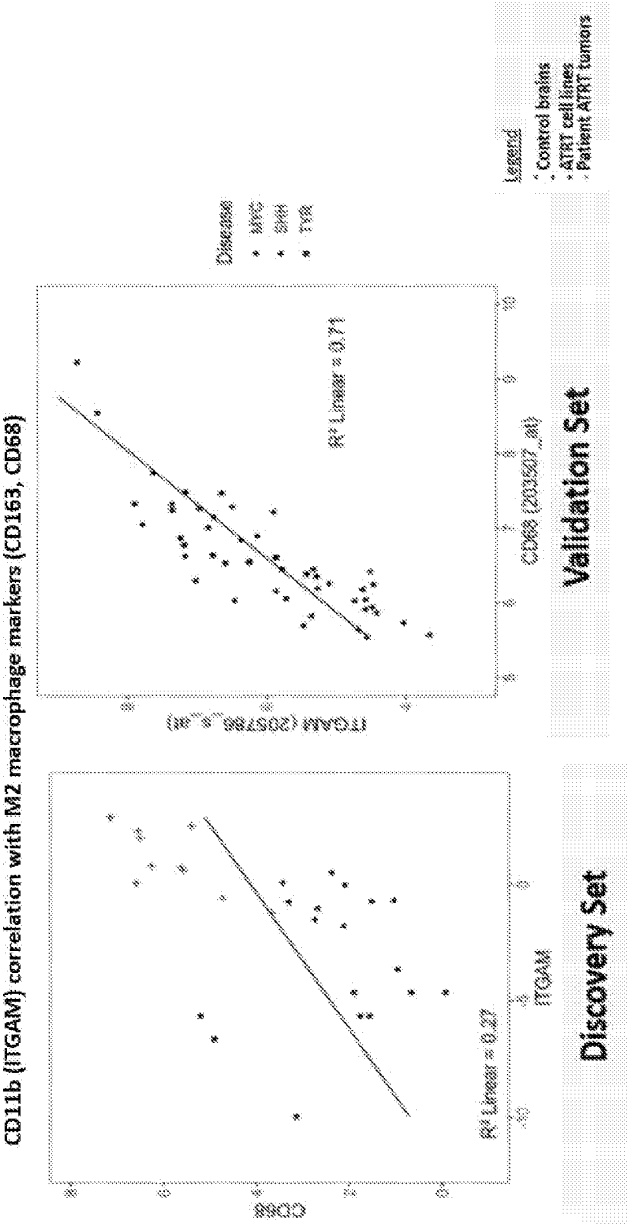
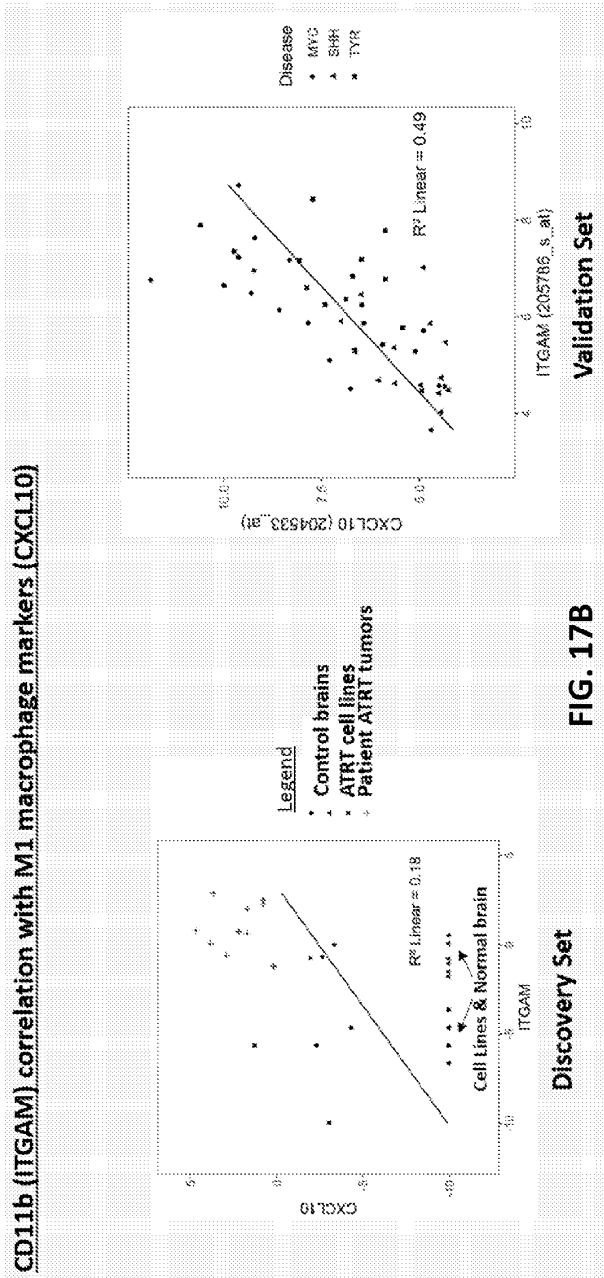


FIG. 17A



Correlation between M2 macrophage markers (CD163, CD68)

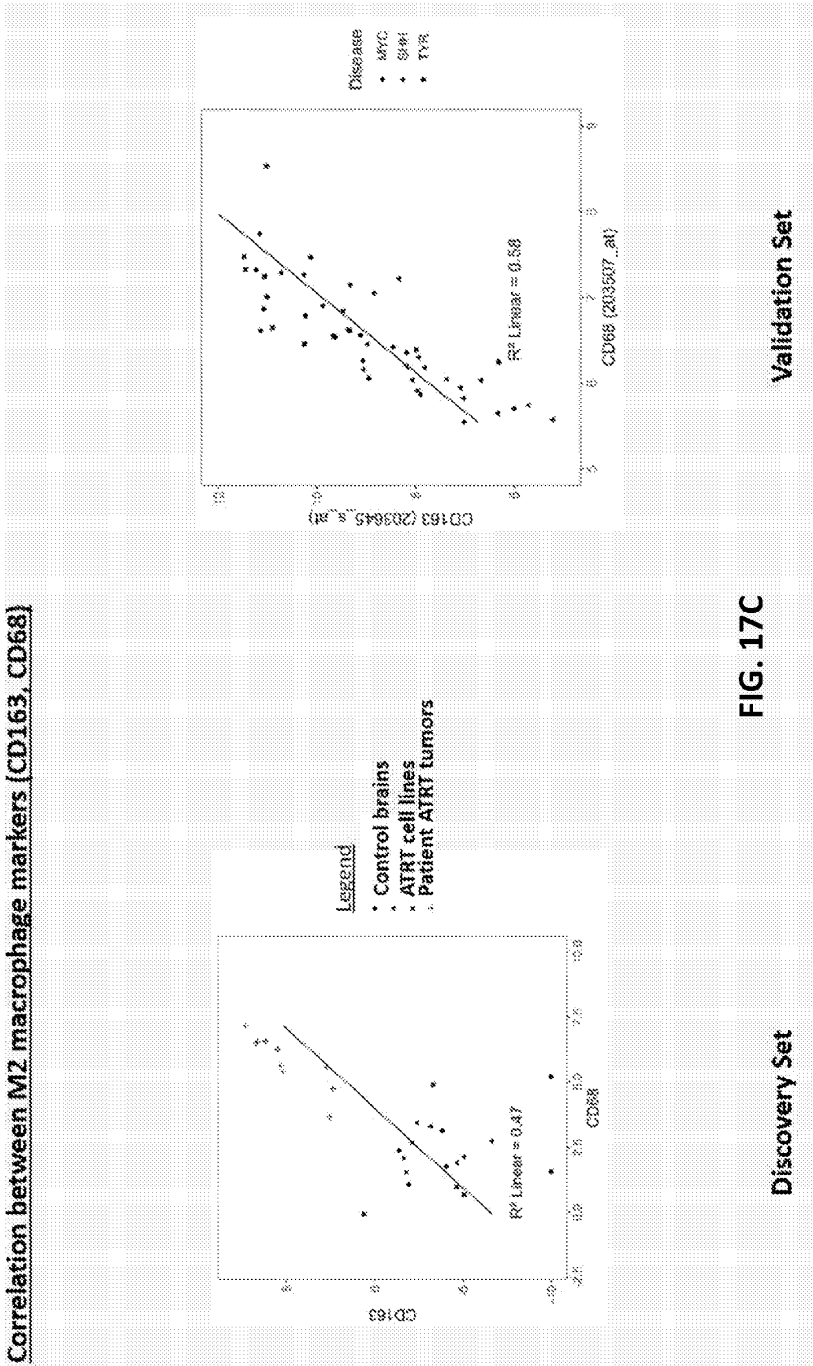


FIG. 17C

M1 macrophage marker (CXCL10) correlation with M2 macrophage marker (CD163 & CD68)

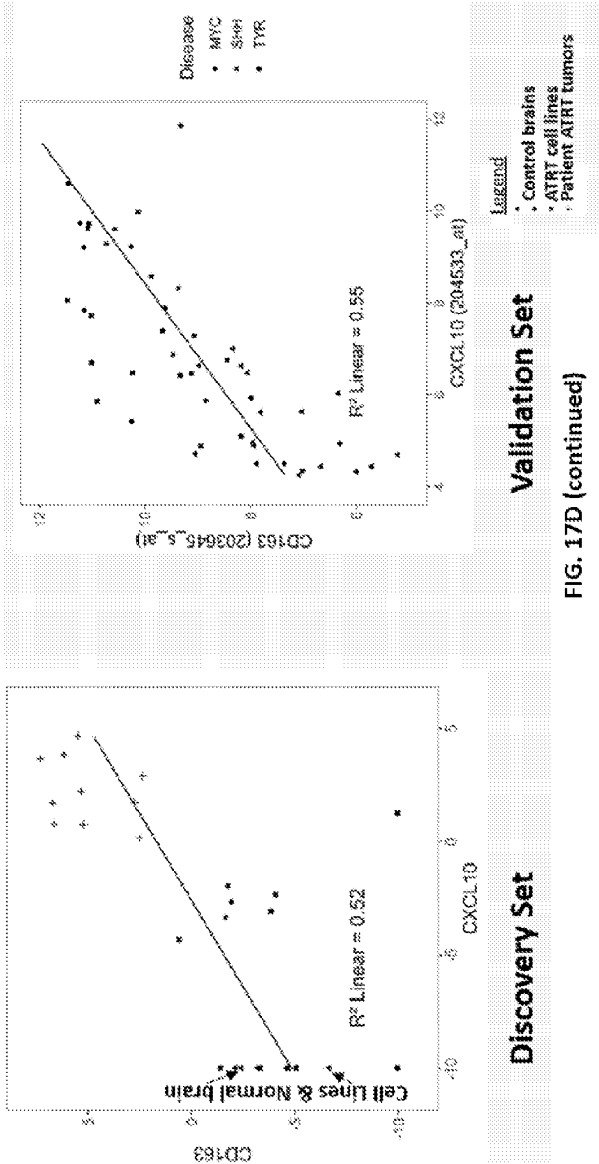


FIG. 17D (continued)

M1 macrophage marker (CXCL10) correlation with M2 macrophage marker (CD163 & CD68)

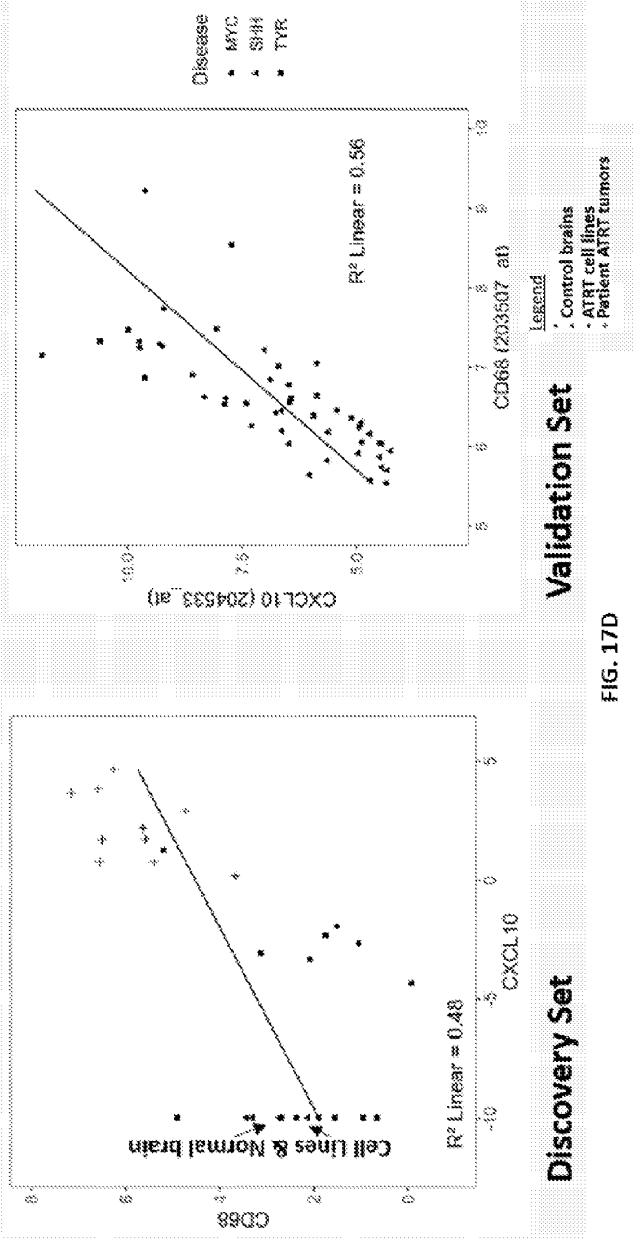


FIG. 17D



Discovery Set (n=28)

Comparison of CD11b (ITGAM) & CD163 expression among Patient Tumors, ATRT Cell Lines, Fetal and Childhood normal brain controls

| Gene Symbol | p-value  | Fold Change (Tumor vs Fetal brain control) |               | Tumor/Fetal Control | p-value | Fold Change (Tumor vs Tumor/Cell Lines/lines) |               | Tumor/Cell lines/Cell lines/lines/Control | p-value     | Fold Change (Cell lines vs Childhood Tumor/Childhood lines/Childhood lines/Control) |               | p-value     | Fold Change (Tumor vs All brain controls/brain controls) |               | Tumor/All brain controls/brain controls |
|-------------|----------|--------------------------------------------|---------------|---------------------|---------|-----------------------------------------------|---------------|-------------------------------------------|-------------|-------------------------------------------------------------------------------------|---------------|-------------|----------------------------------------------------------|---------------|-----------------------------------------|
|             |          | Upregulated                                | Downregulated |                     |         | Upregulated                                   | Downregulated |                                           |             | Upregulated                                                                         | Downregulated |             | Upregulated                                              | Downregulated |                                         |
| CD163       | 8.03E-05 | 107.065                                    | Upregulated   | 5.32E-09            | 1993.15 | Upregulated                                   | 1.04E-07      | 532.584                                   | Upregulated | 1.427746                                                                            | 2.033274      | Upregulated | 1.59E-07                                                 | 2.35.6811     | Upregulated                             |
| ITGAM       | 0.187204 | 2.35113                                    | Unregulated   | 1.82E-09            | 112.44  | Unregulated                                   | 0.00329673    | 5.12465                                   | Unregulated | 0.59E-05                                                                            | 18.2386       | Unregulated | 0.0166284                                                | 3.75714       | Unregulated                             |

Validation Set (n=49)

Comparison of CD163 expression among ATRT-Subtypes

| Probeset ID | Gene Symbol | Fold Change (MYC vs SHH and TYR) |                       | Fold Change (SHH vs MYC and TYR) |                         | Fold Change (TYR vs MYC and SHH) |                       |
|-------------|-------------|----------------------------------|-----------------------|----------------------------------|-------------------------|----------------------------------|-----------------------|
|             |             | p-value                          | Description           | p-value                          | Description             | p-value                          | Description           |
| 203645_s_at | CD163       | 0.0122979                        | MYC up vs SHH and TYR | 8.56E-06                         | SHH down vs MYC and TYR | 0.00902573                       | TYR up vs MYC and SHH |

Validation Set (n=49)

Comparison of CD11b (ITGAM) expression among ATRT-Subtypes

| Probeset ID | Gene Symbol | Fold Change (MYC vs SHH and TYR) |                       | Fold Change (SHH vs MYC and TYR) |                         | Fold Change (TYR vs MYC and SHH) |                       |
|-------------|-------------|----------------------------------|-----------------------|----------------------------------|-------------------------|----------------------------------|-----------------------|
|             |             | p-value                          | Description           | p-value                          | Description             | p-value                          | Description           |
| 205785_s_at | ITGAM       | 0.102953                         | MYC up vs SHH and TYR | 0.50324388                       | SHH down vs MYC and TYR | 0.134013                         | TYR up vs MYC and SHH |

FIG. 17E

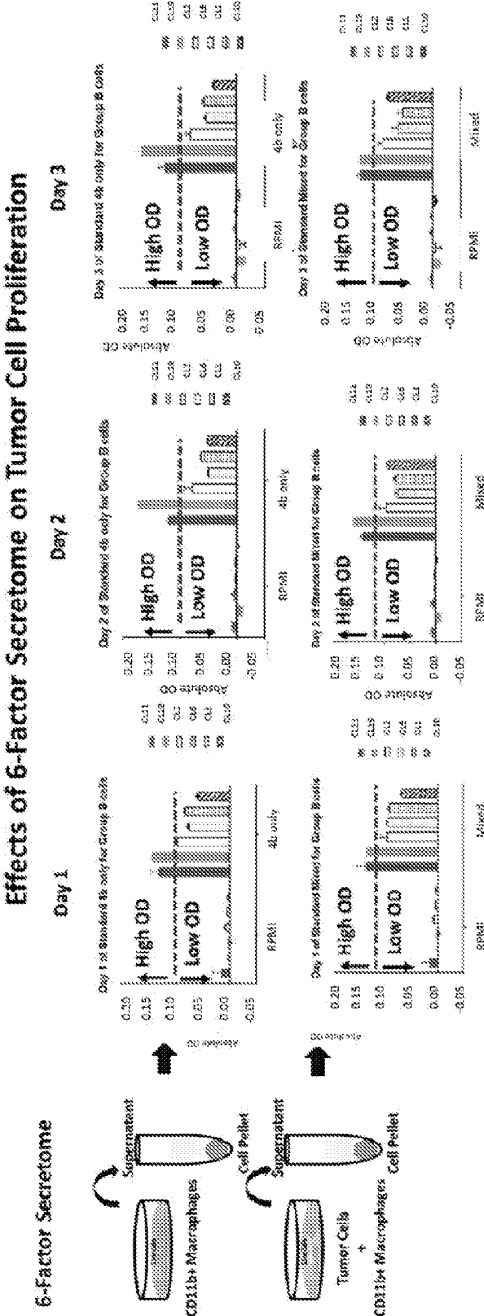
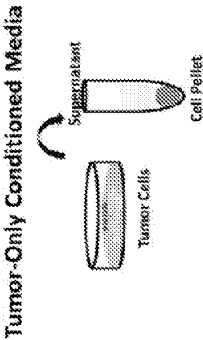
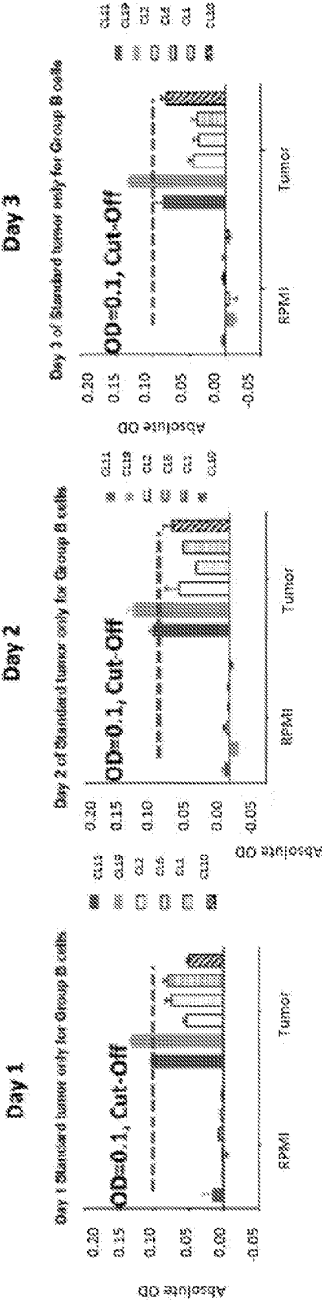


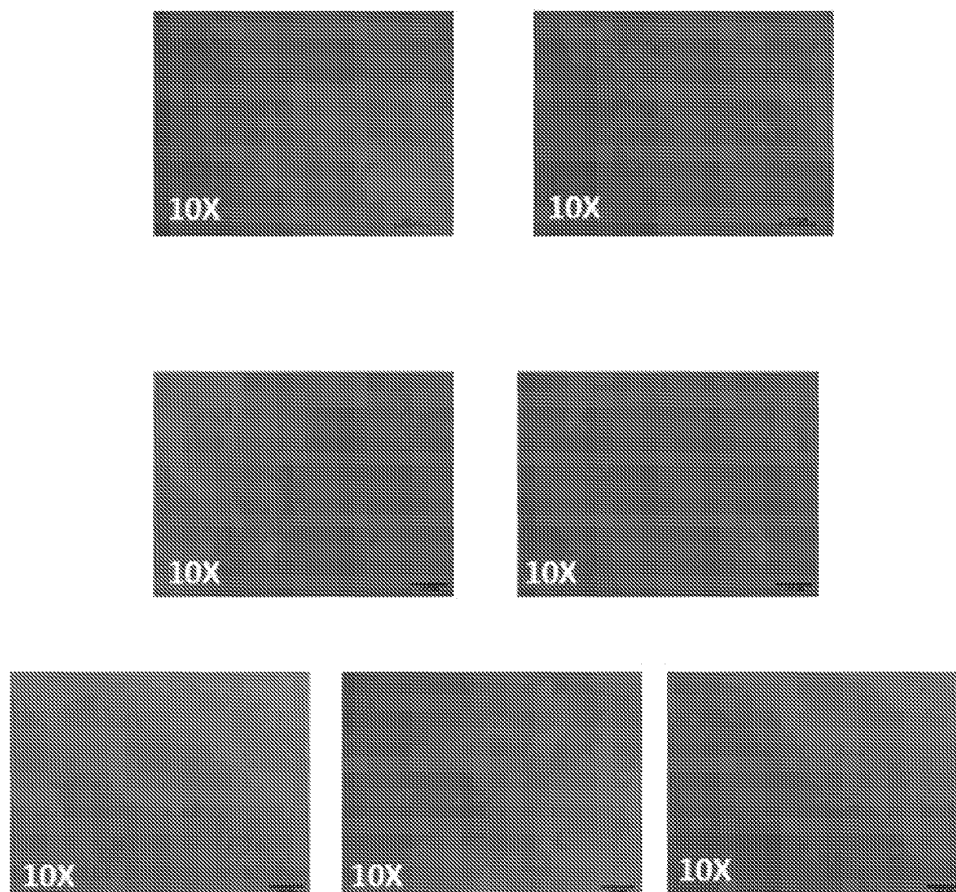
FIG. 18A (continued)



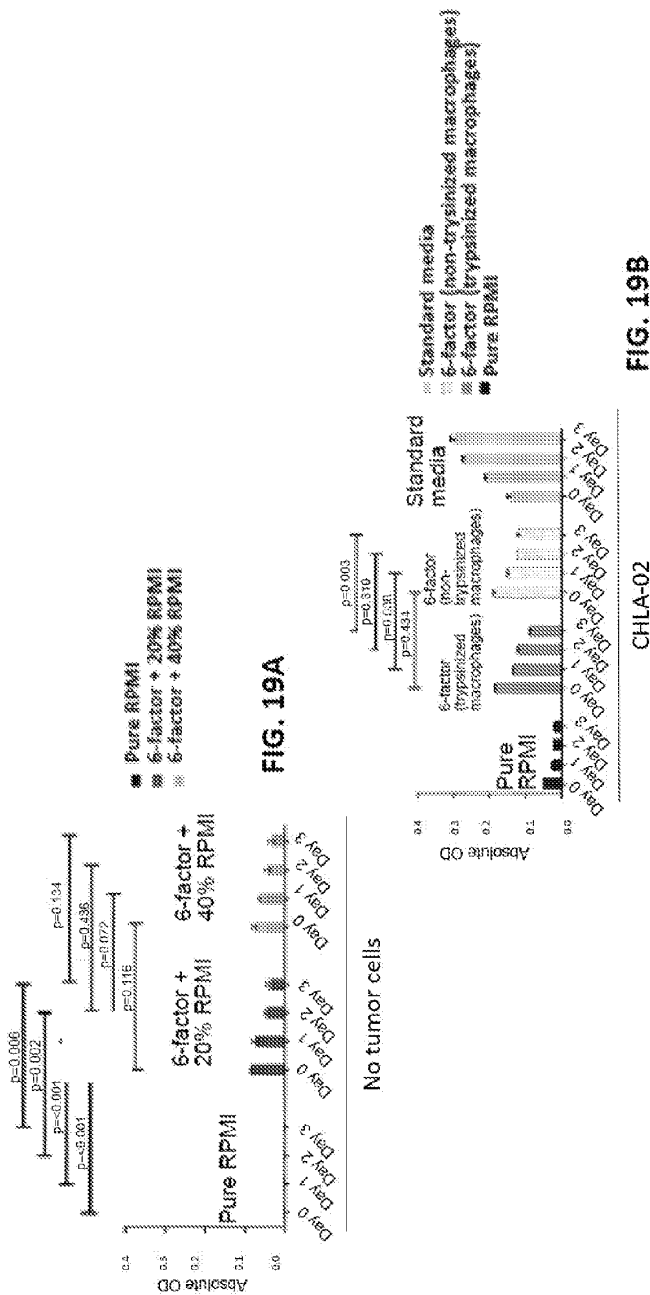
**Effects of Tumor-Only Conditioned Media on Tumor Cell Proliferation**



**FIG. 18A**



**FIG. 18B**



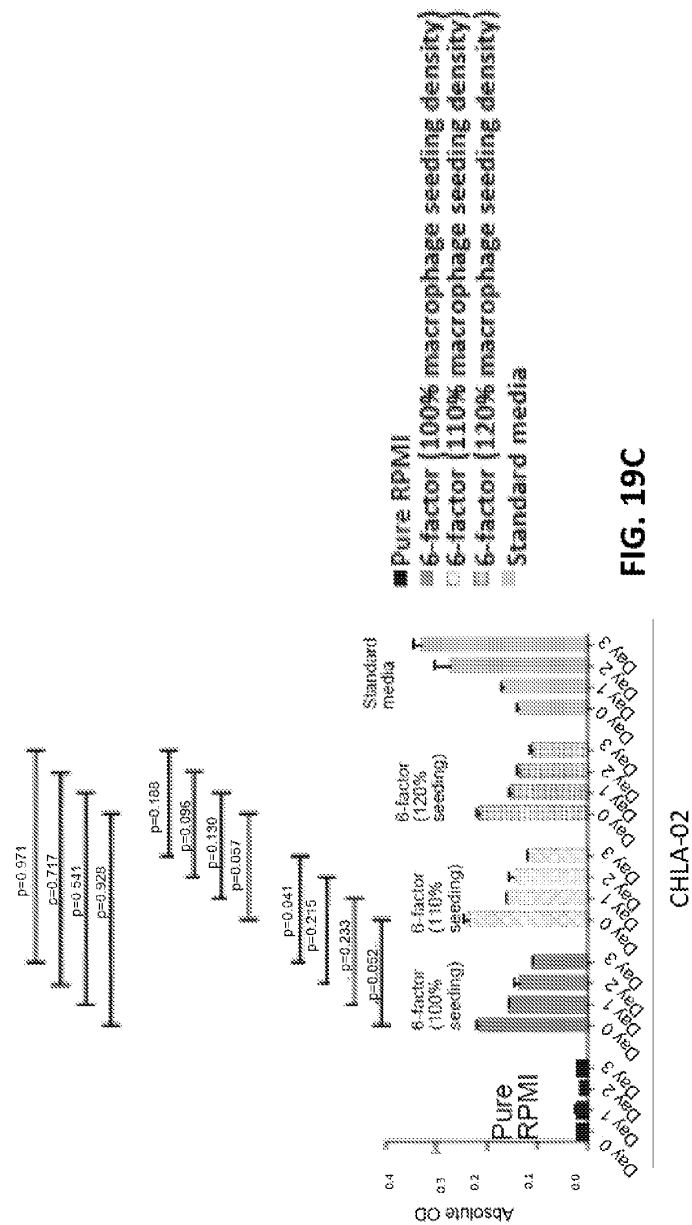
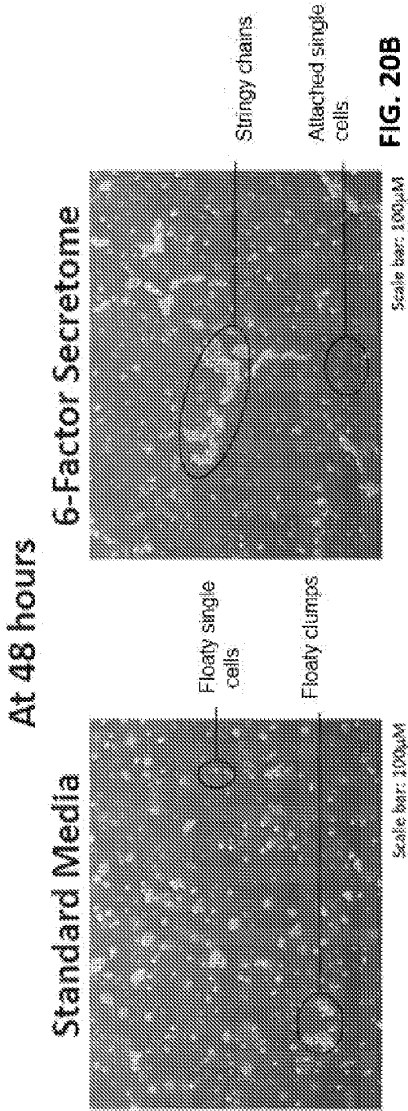
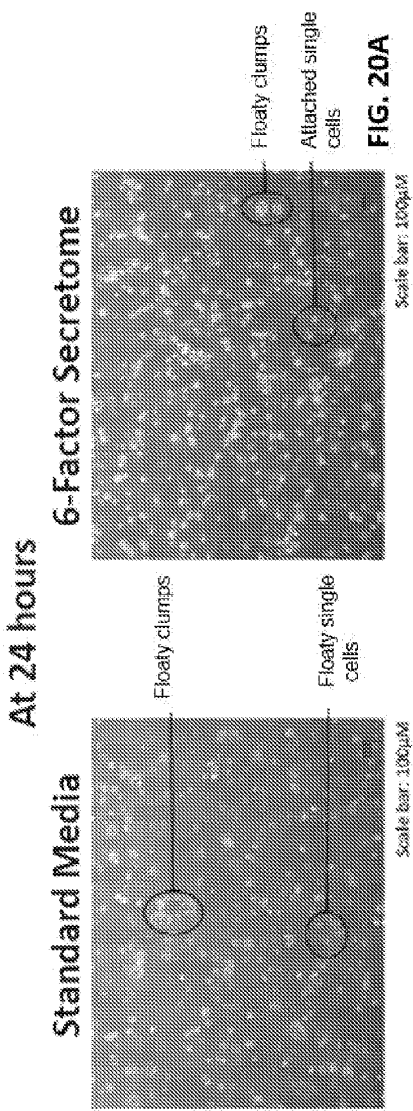
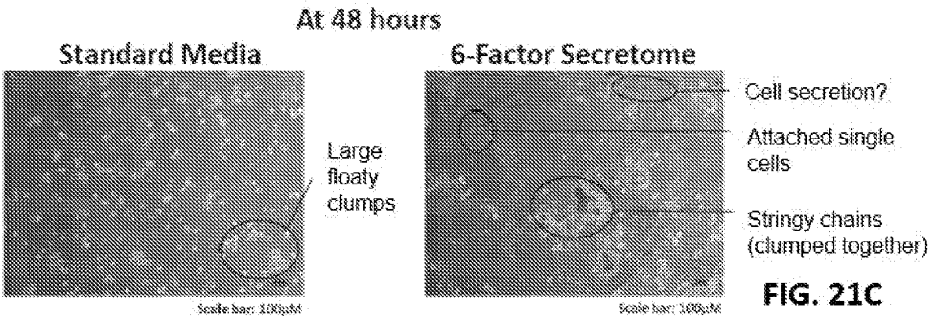
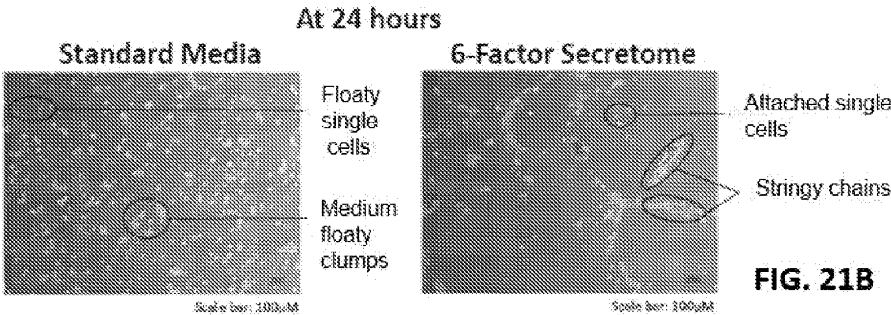
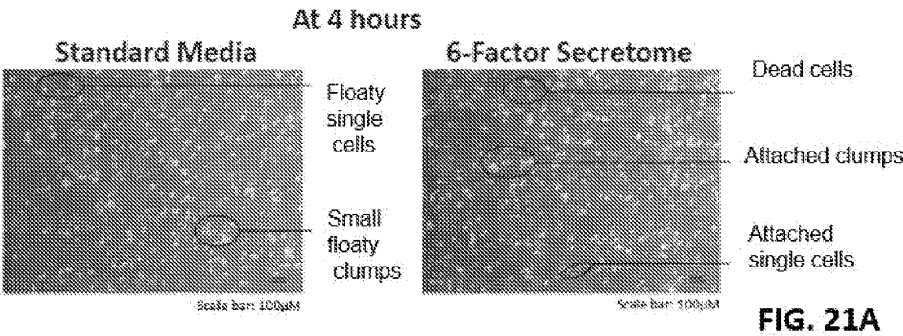
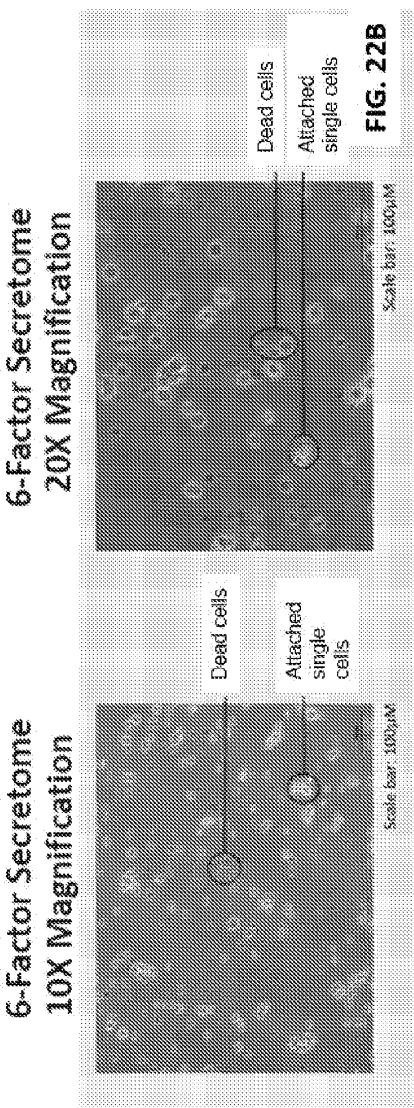
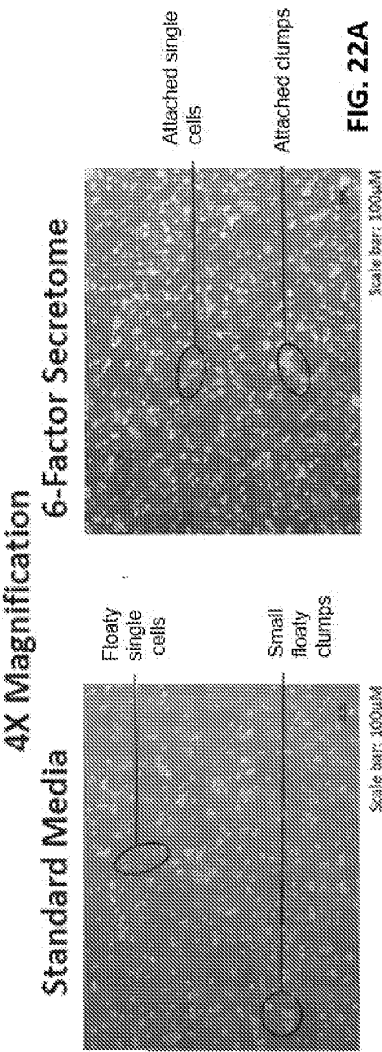


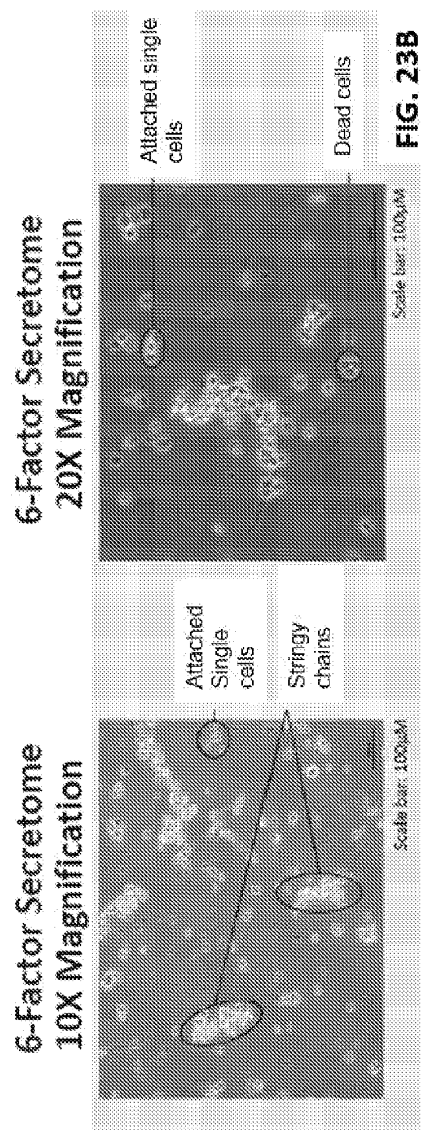
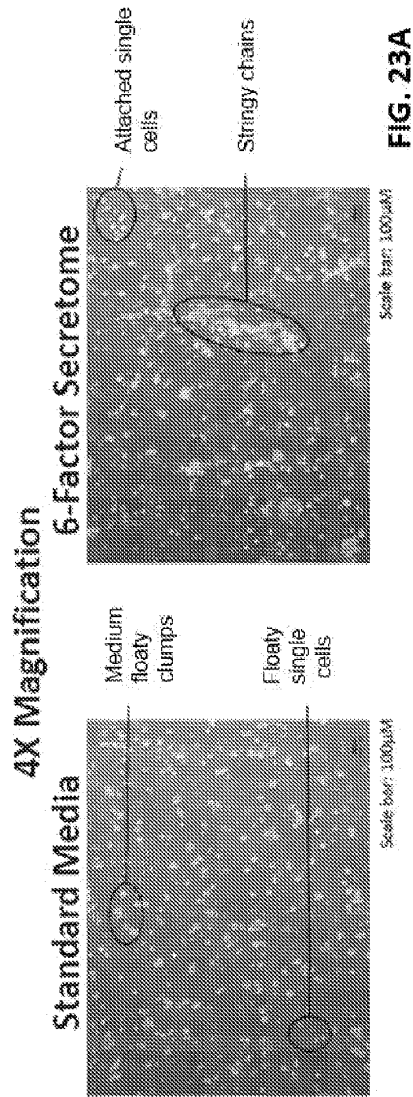
FIG. 19C

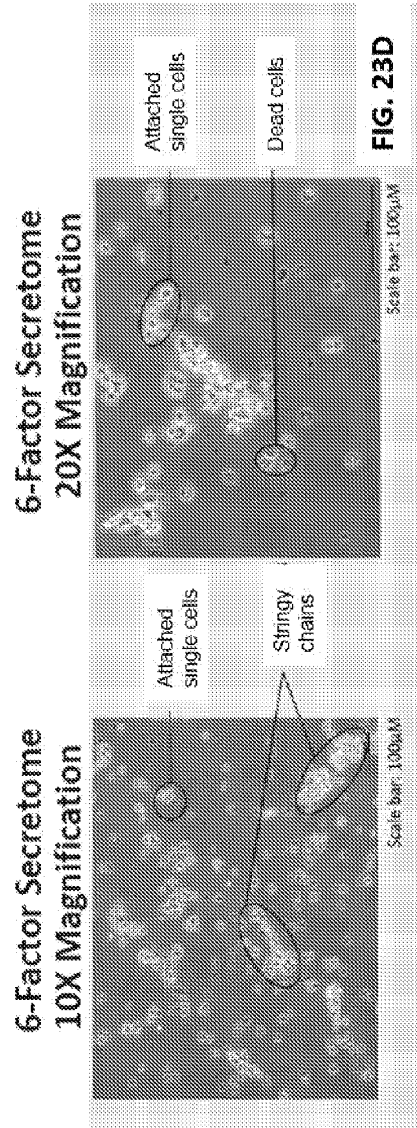
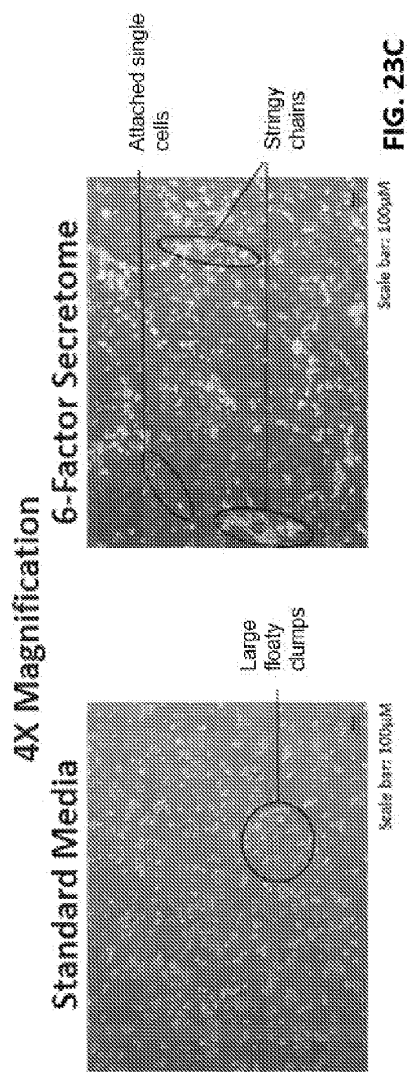


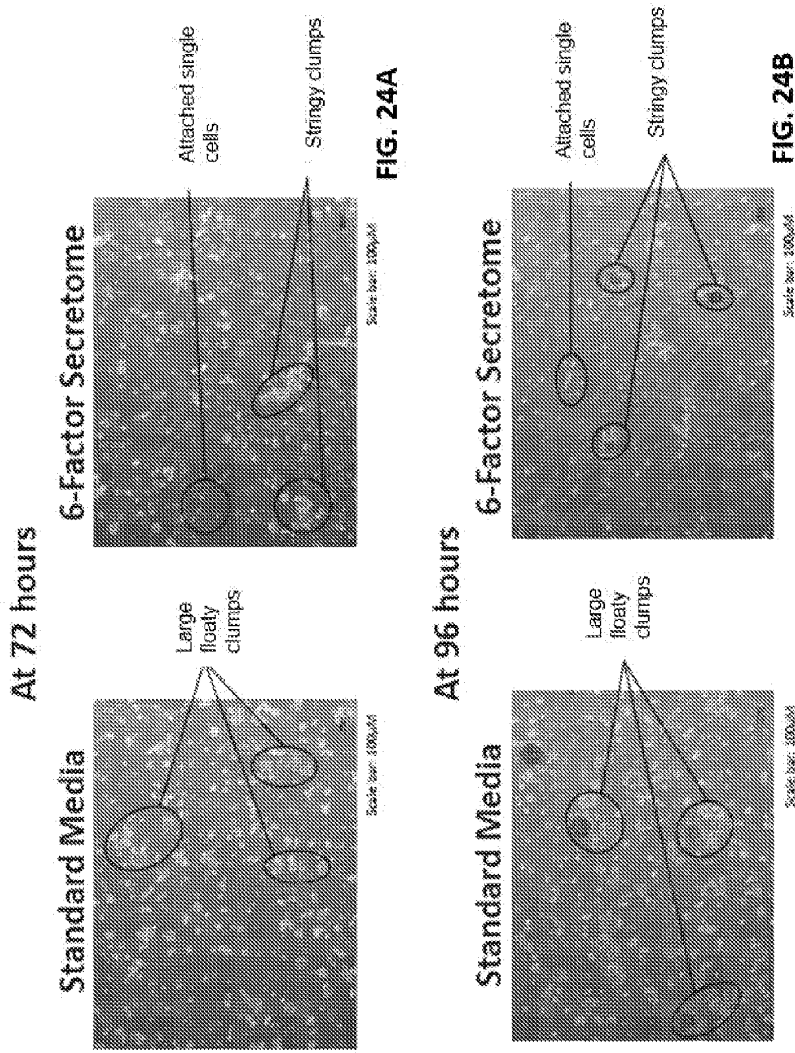


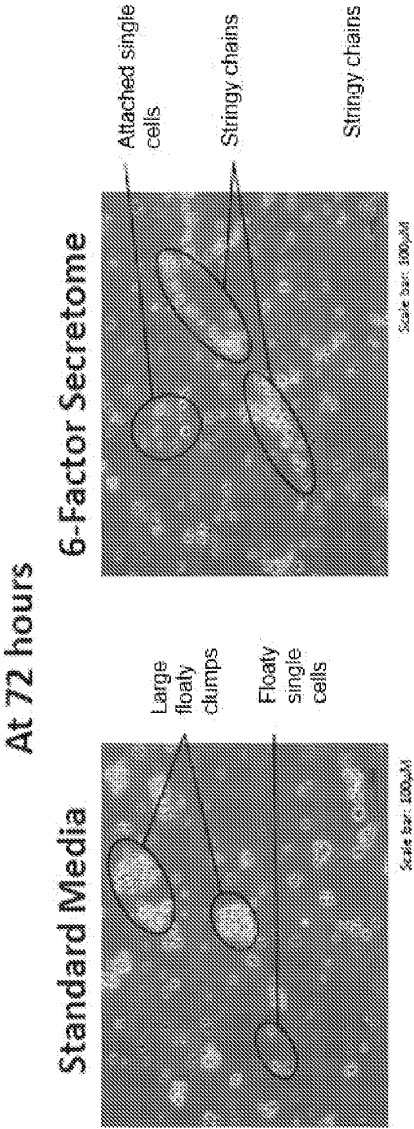




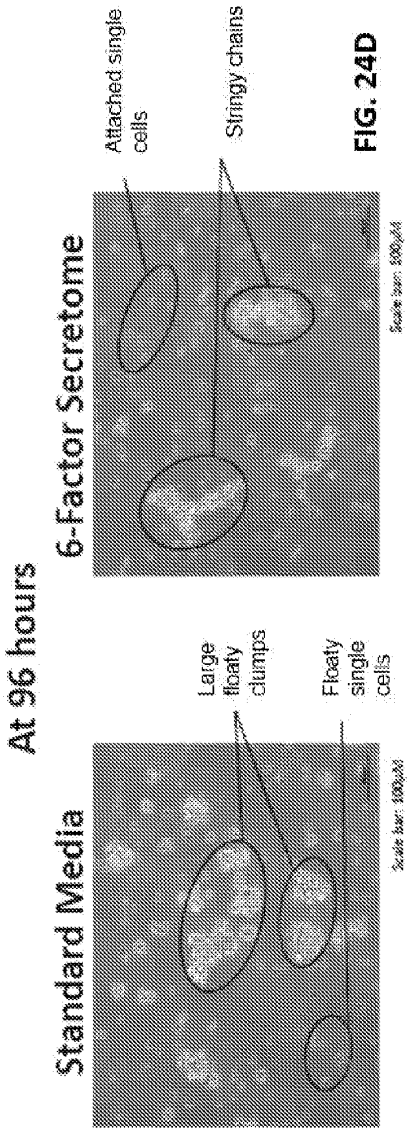




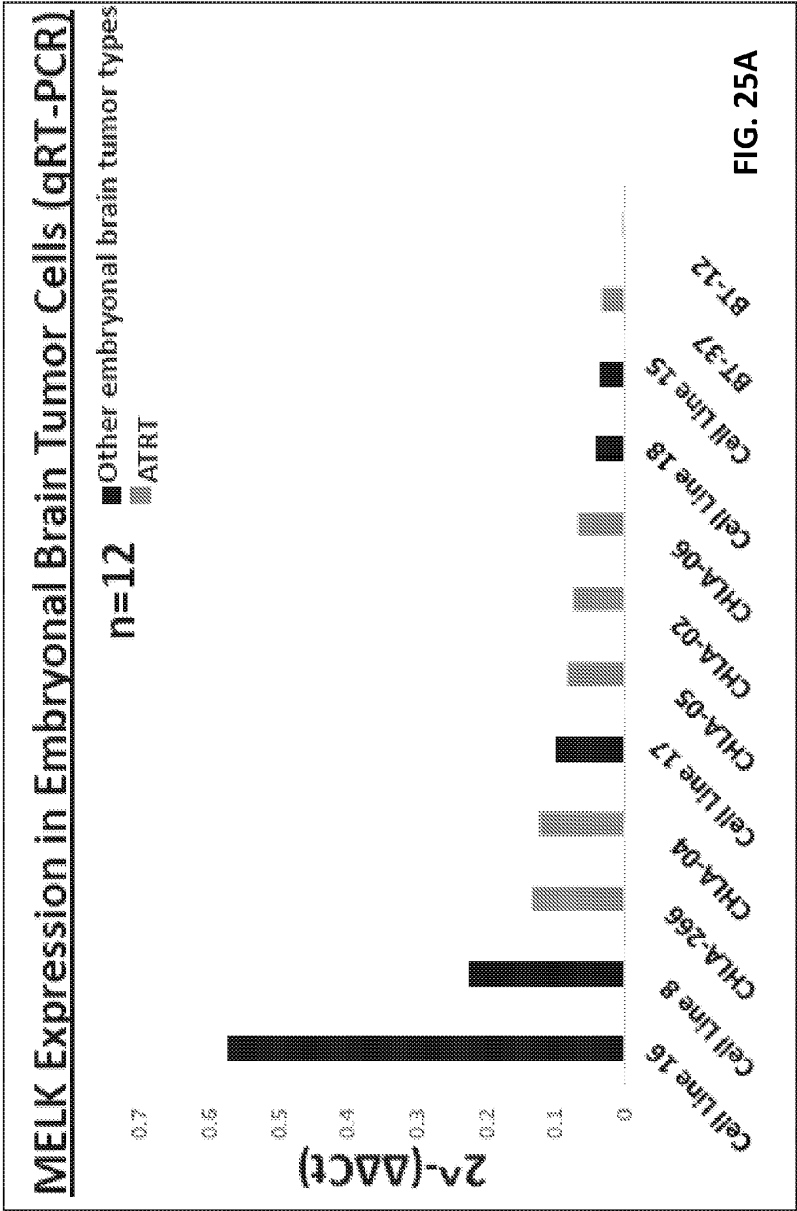




**FIG. 24C**



**FIG. 24D**



Discovery Set (n=28)

Comparison of MELK expression among patient tumors, AIRT cell lines, fetal and childhood normal brain controls

| MELK | p-value[Patient tumors vs. Childhood brains] | p-value[Patient tumors vs. Cell lines] | p-value[Patient tumors vs. fetal brains] | p-value[cell lines vs. all brains] | p-value[patient tumors vs. all brains] |
|------|----------------------------------------------|----------------------------------------|------------------------------------------|------------------------------------|----------------------------------------|
|      | 1.45E-07                                     | 0.85392                                | 1.87E-05                                 | 3.21E-05                           | 4.59E-08                               |

Validation Set (n=49)

Comparison of MELK expression among AIRT-Subtypes

| MELK | p-value[MYC vs. SHH] | p-value[MYC vs. TYR] | p-value[SHH vs. TYR] |
|------|----------------------|----------------------|----------------------|
|      | 0.789273             | 0.021531             | 0.031382             |

FIG. 25B

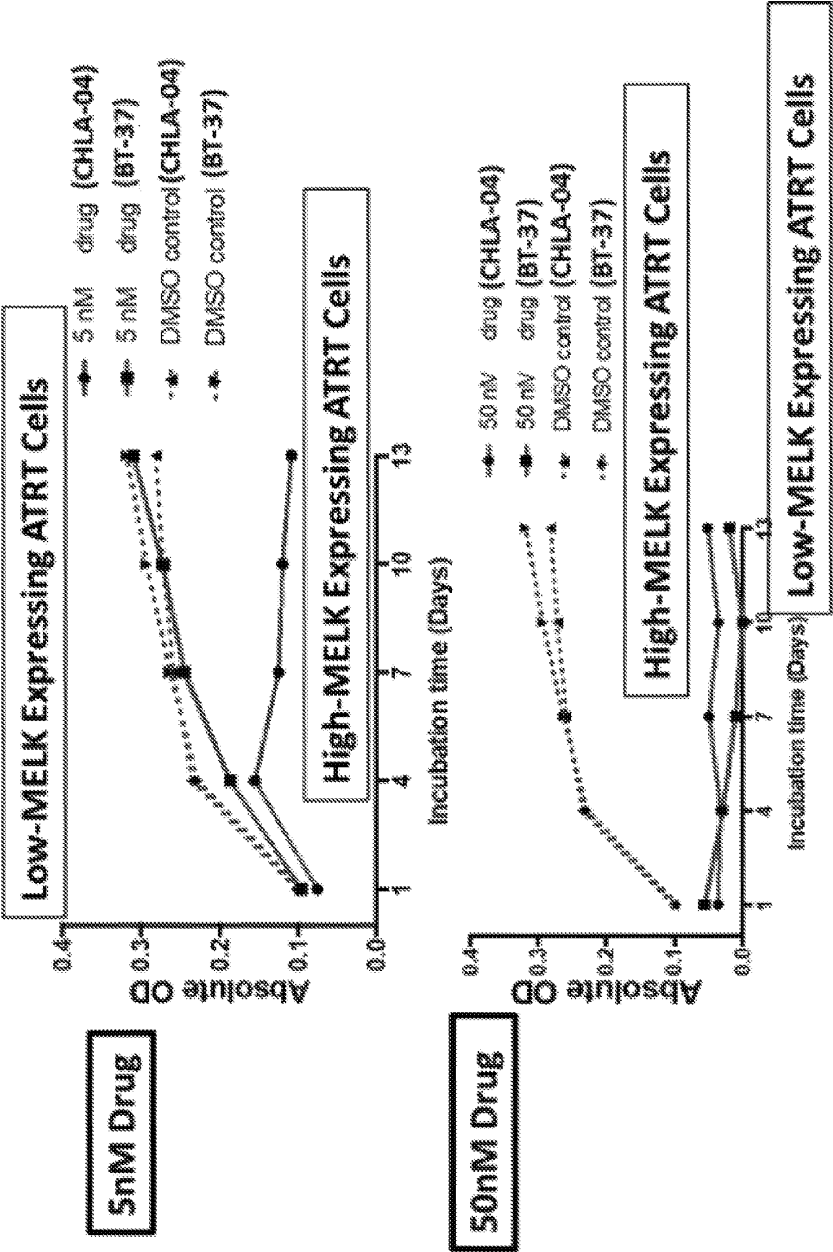
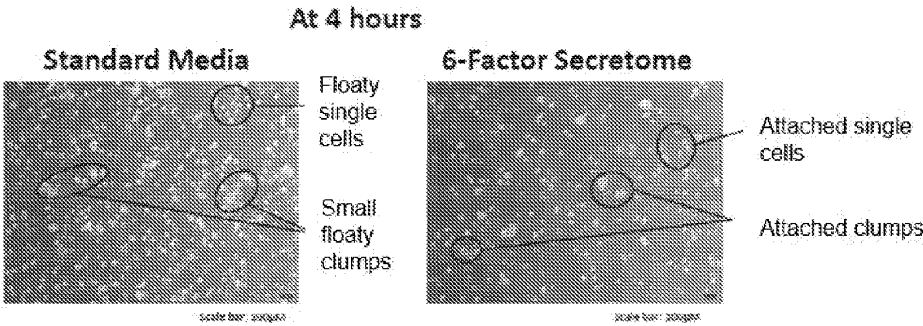
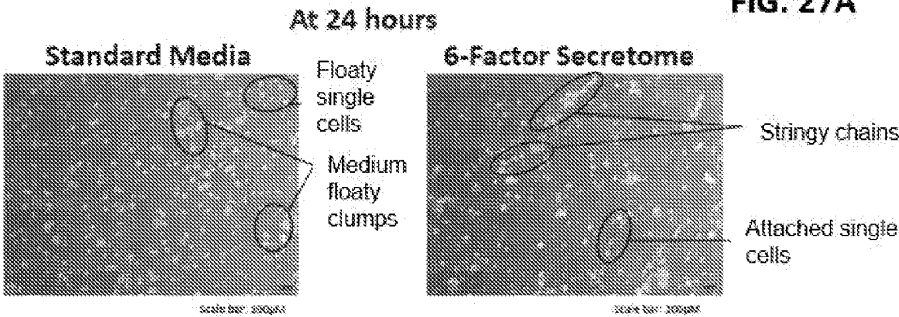


FIG. 26

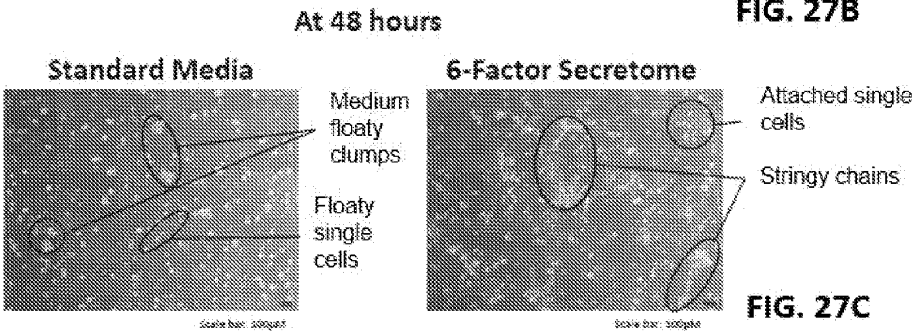




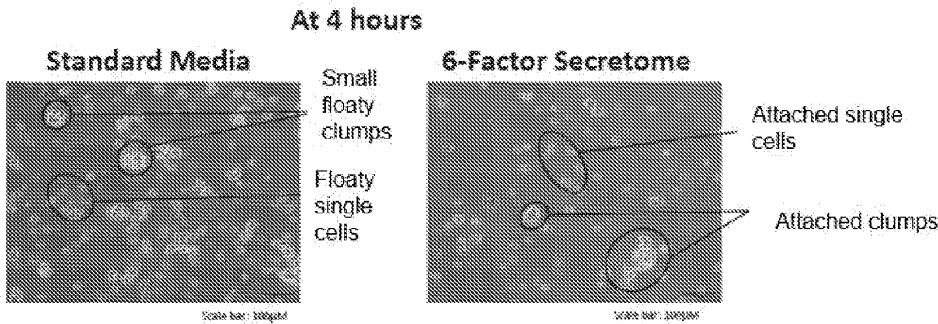
**FIG. 27A**



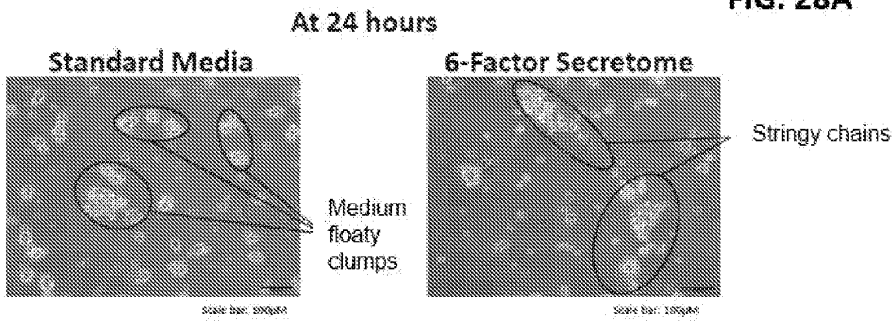
**FIG. 27B**



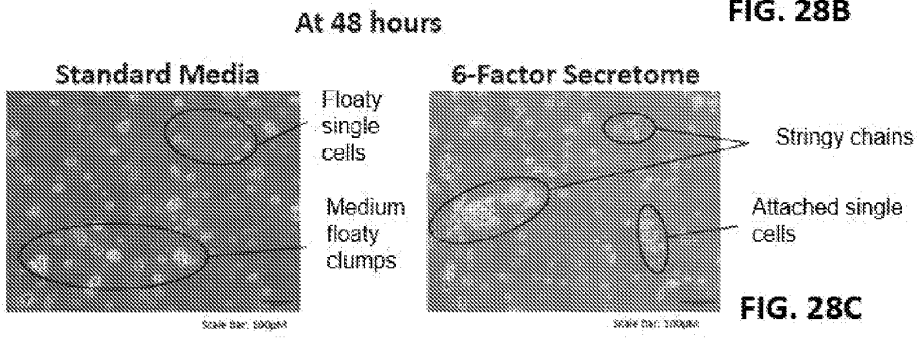
**FIG. 27C**



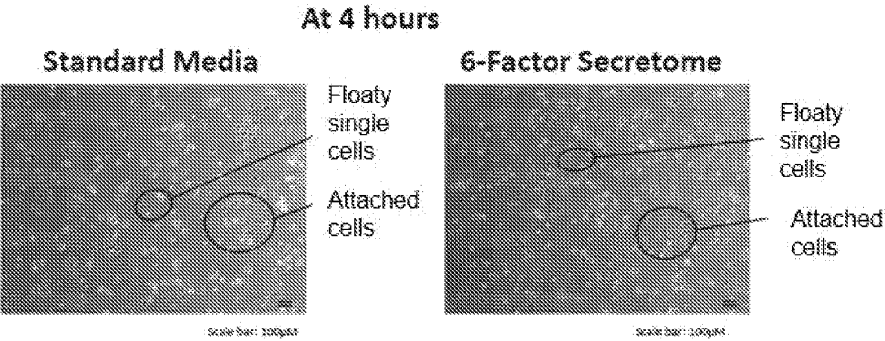
**FIG. 28A**



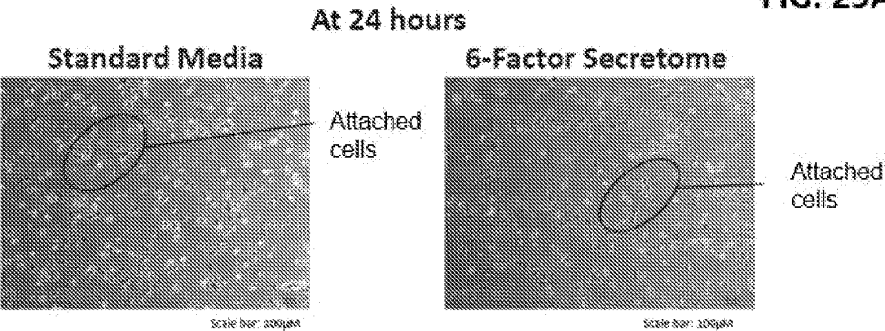
**FIG. 28B**



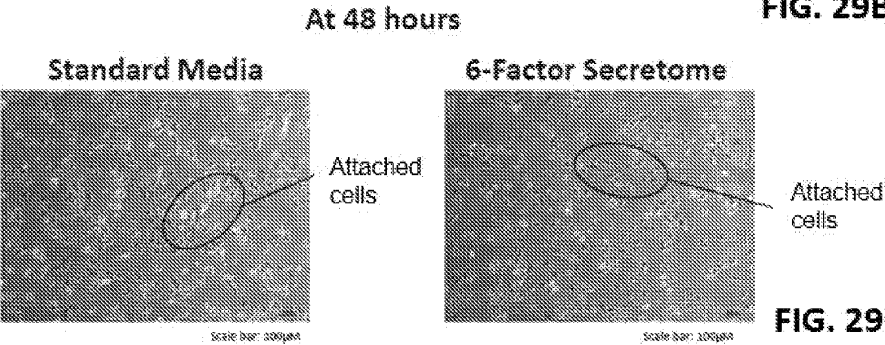
**FIG. 28C**



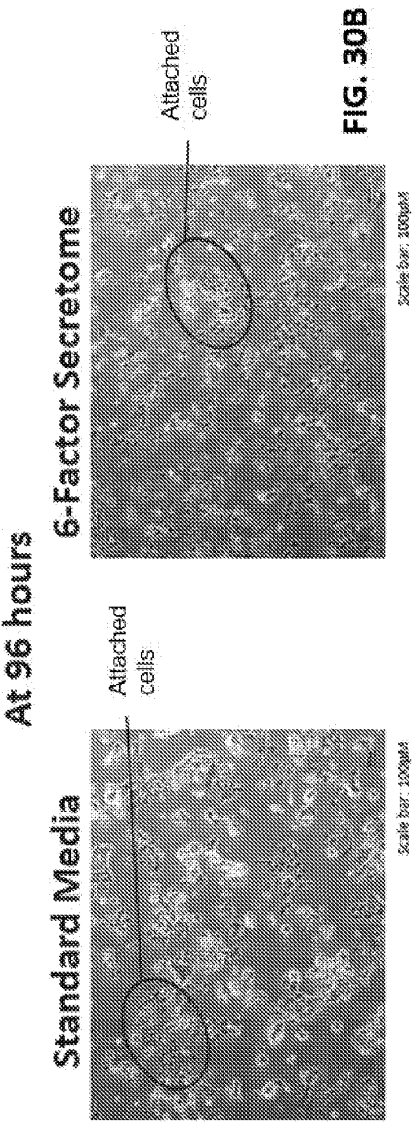
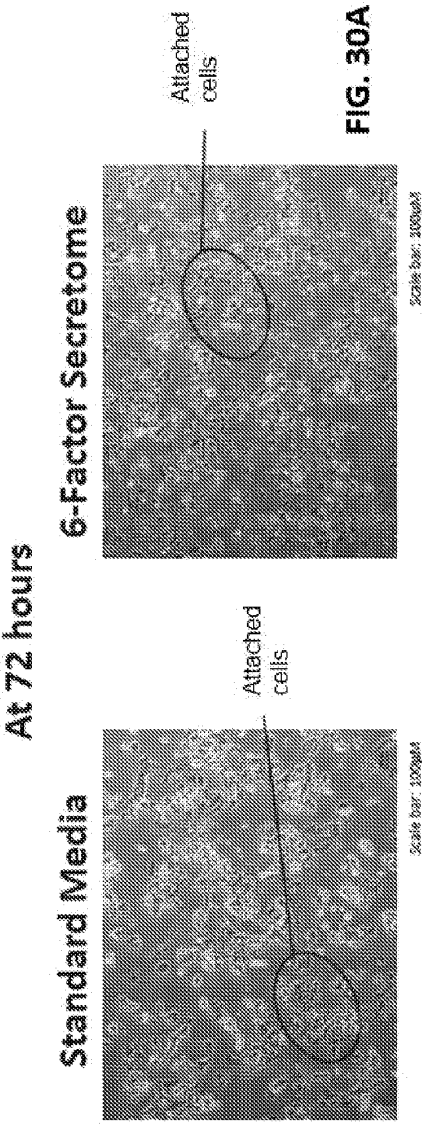
**FIG. 29A**

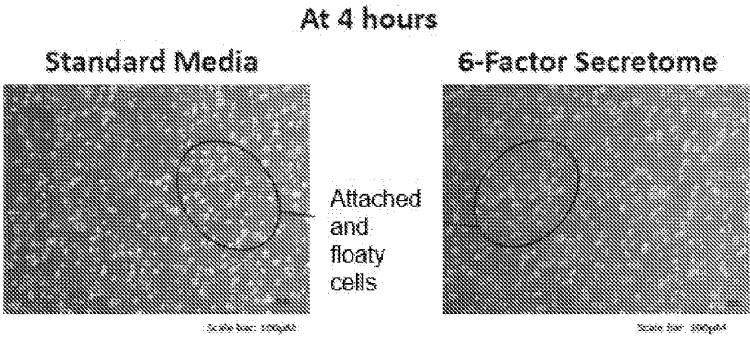


**FIG. 29B**

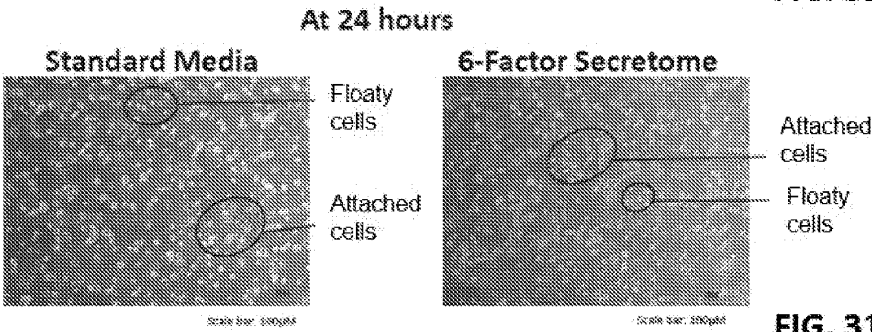


**FIG. 29C**

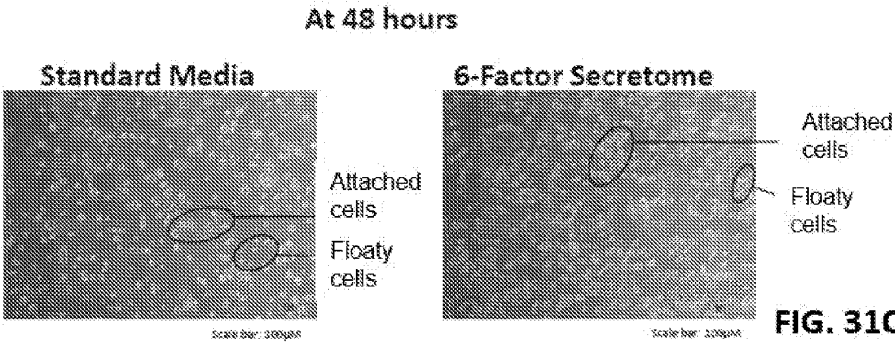




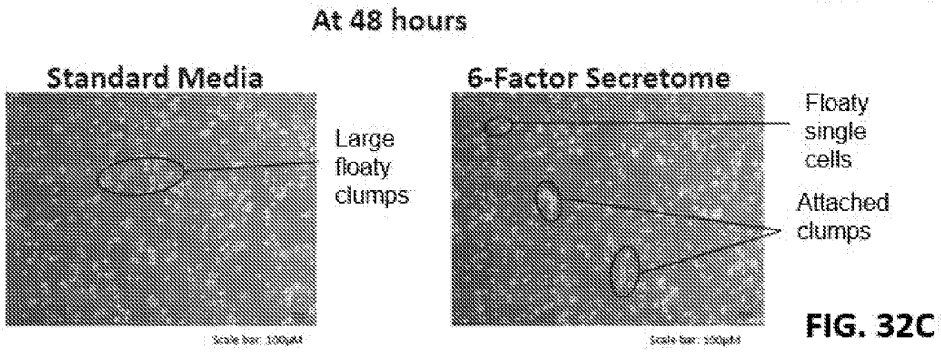
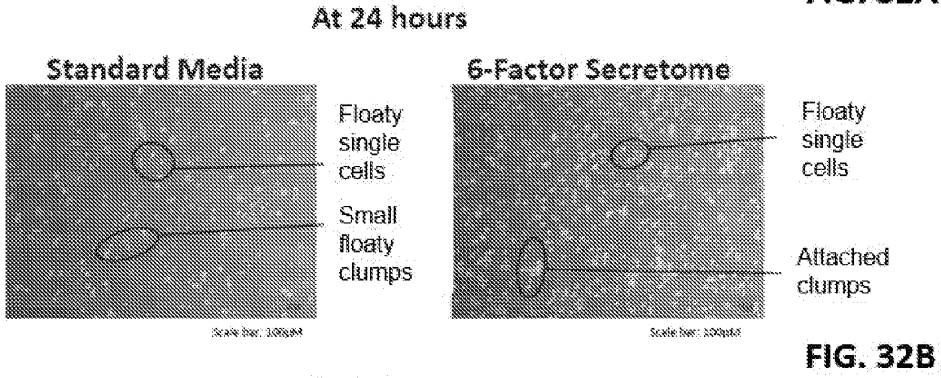
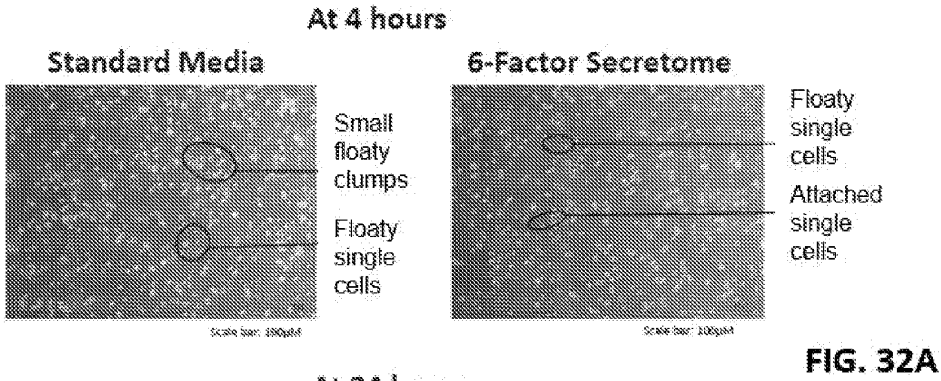
**FIG. 31A**

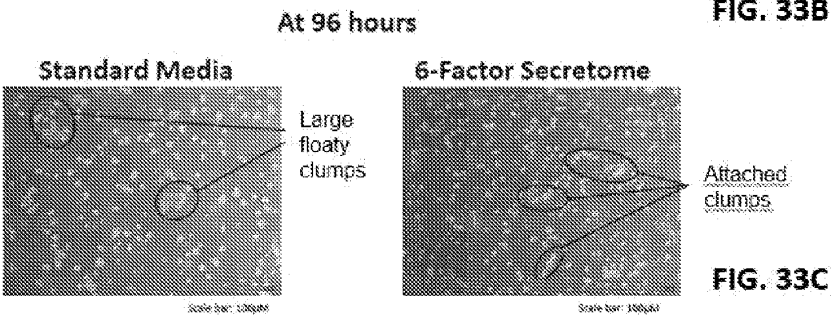
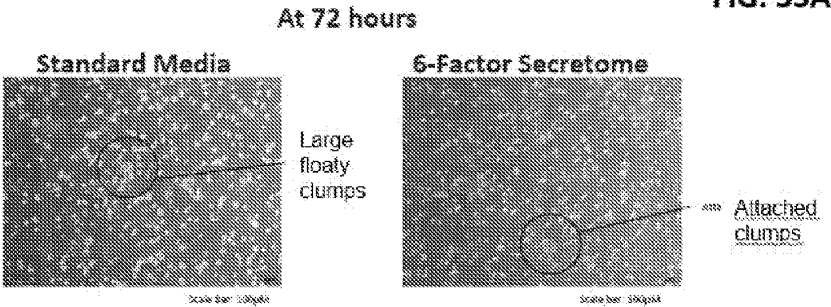
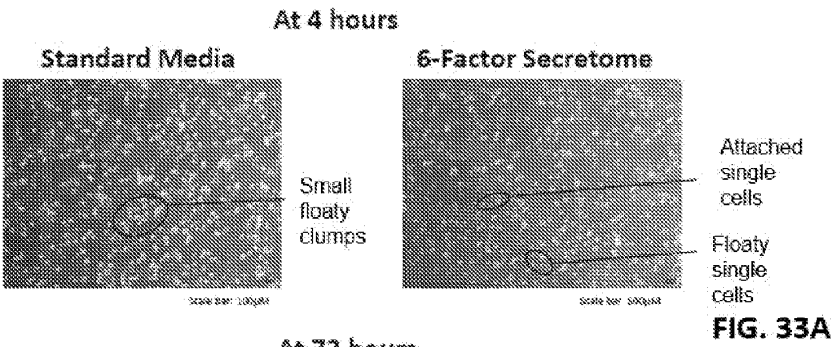


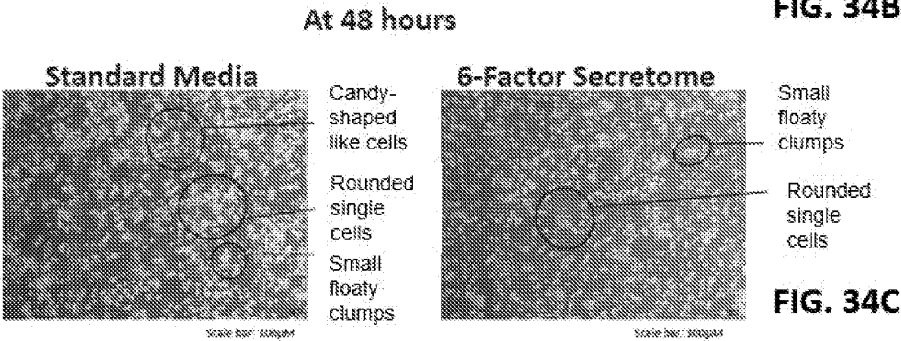
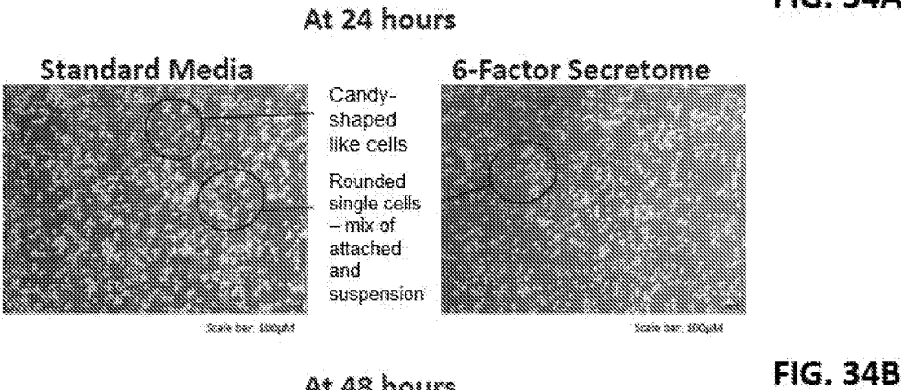
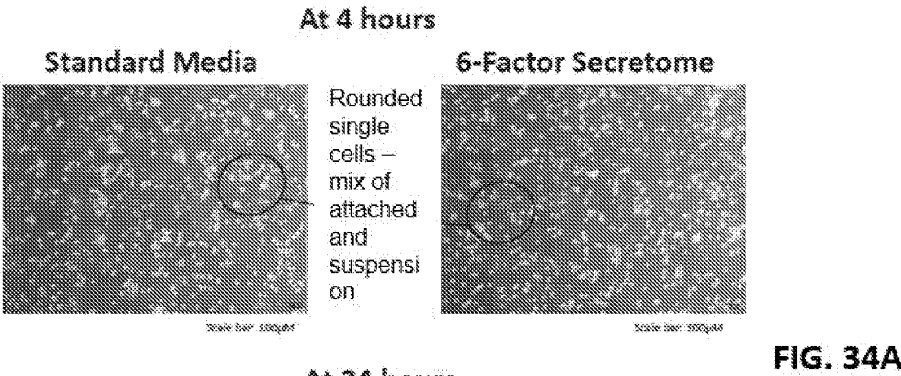
**FIG. 31B**



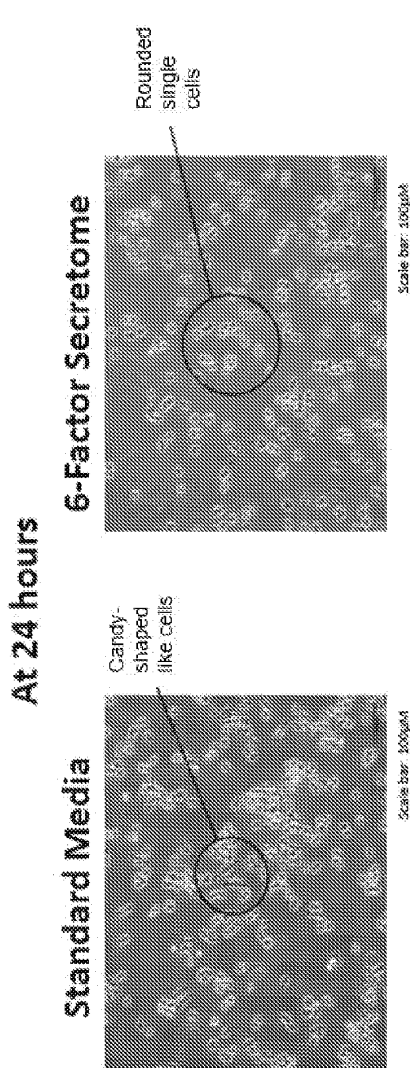
**FIG. 31C**



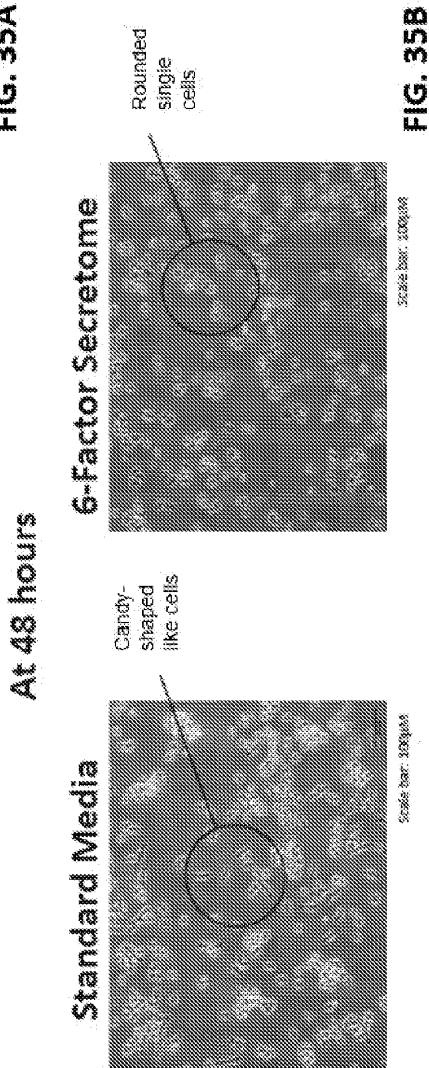








**FIG. 35A**



**FIG. 35B**

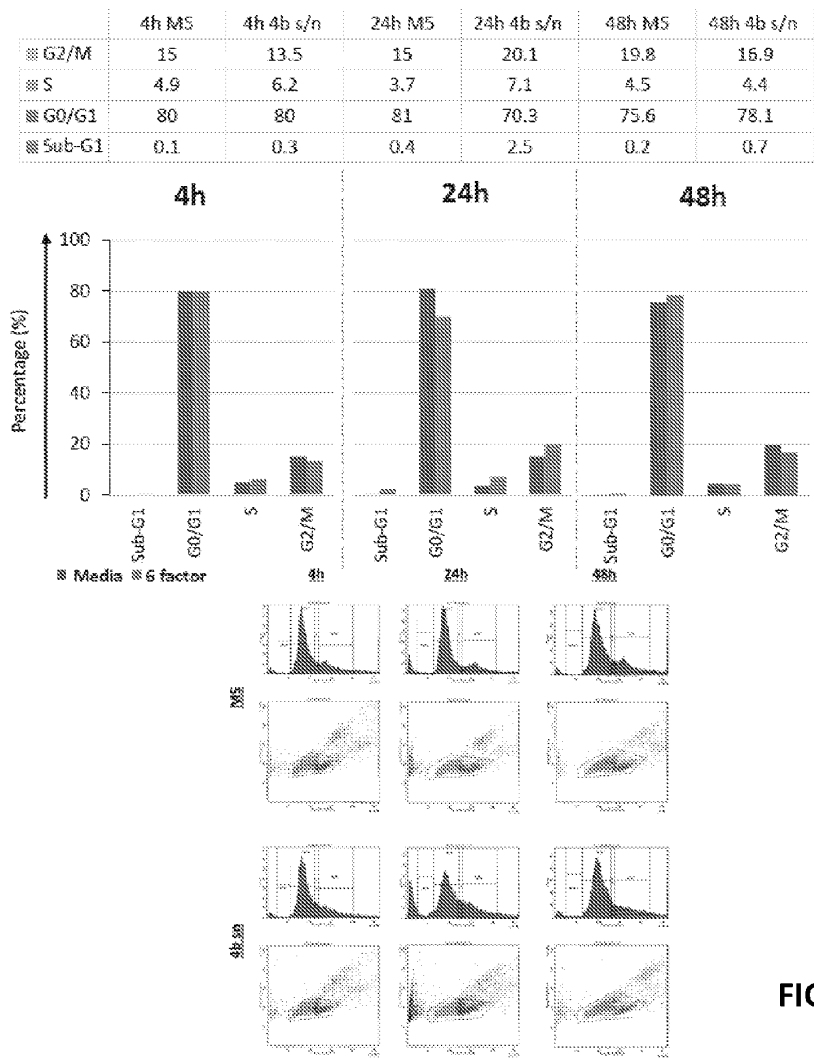


FIG. 36A

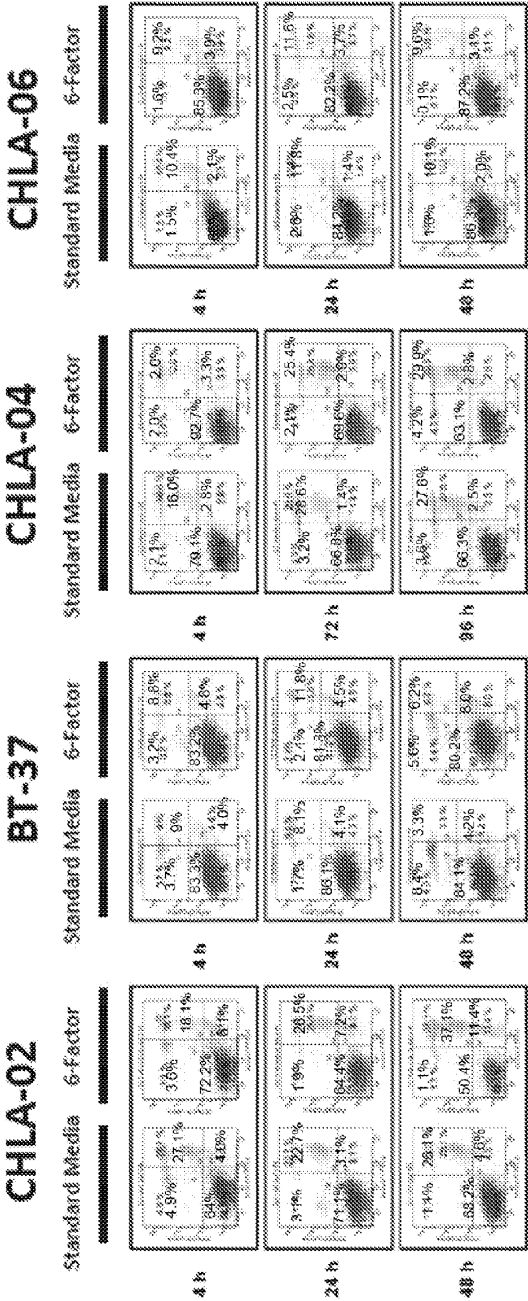


FIG. 36B

FIG. 37A  
(continued)

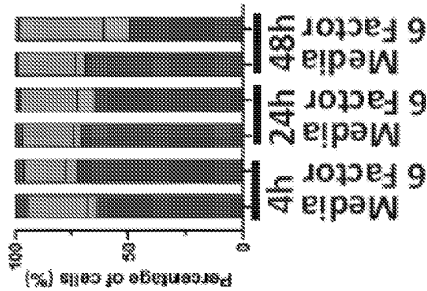


FIG. 37B  
(continued)

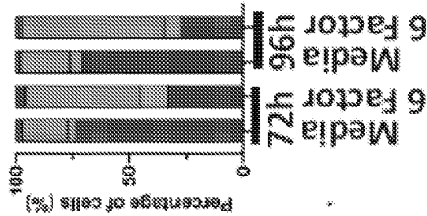


FIG. 37C  
(continued)

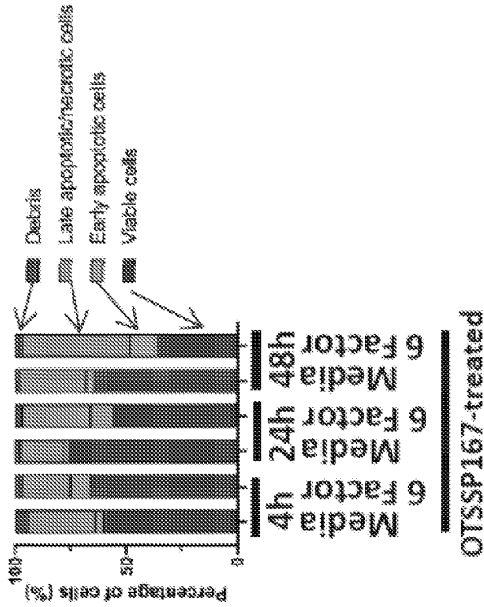


FIG. 37A

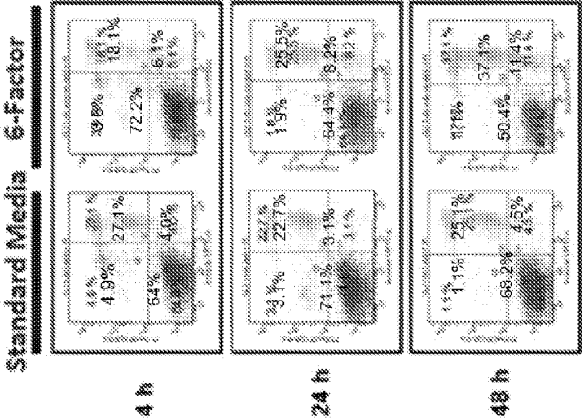


FIG. 37B

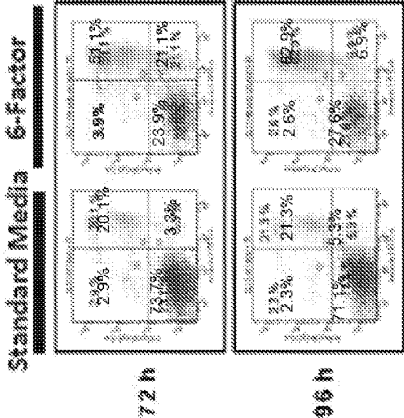


FIG. 37C

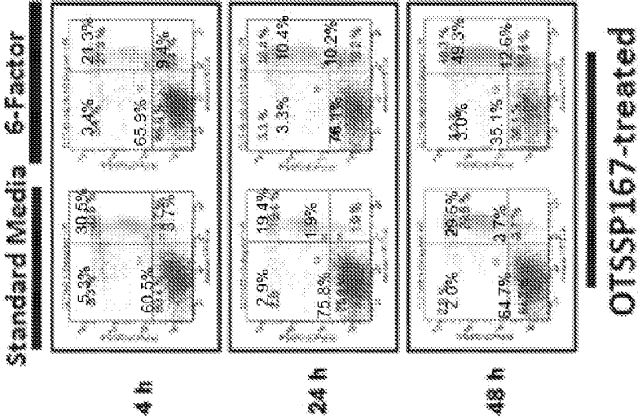


FIG. 38A  
(continued)

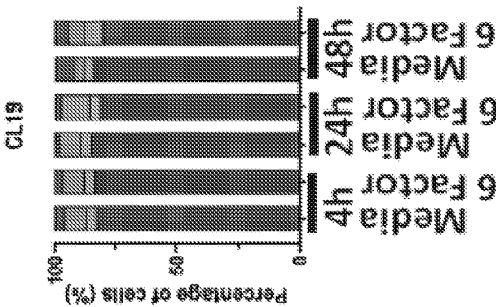


FIG. 38B  
(continued)

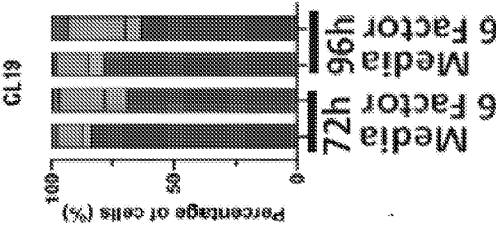
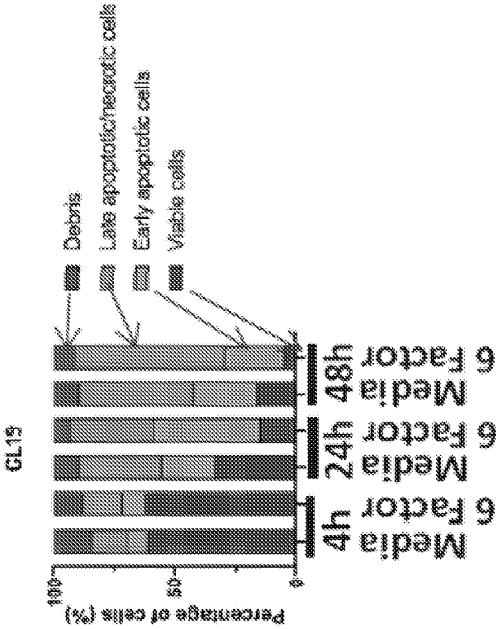
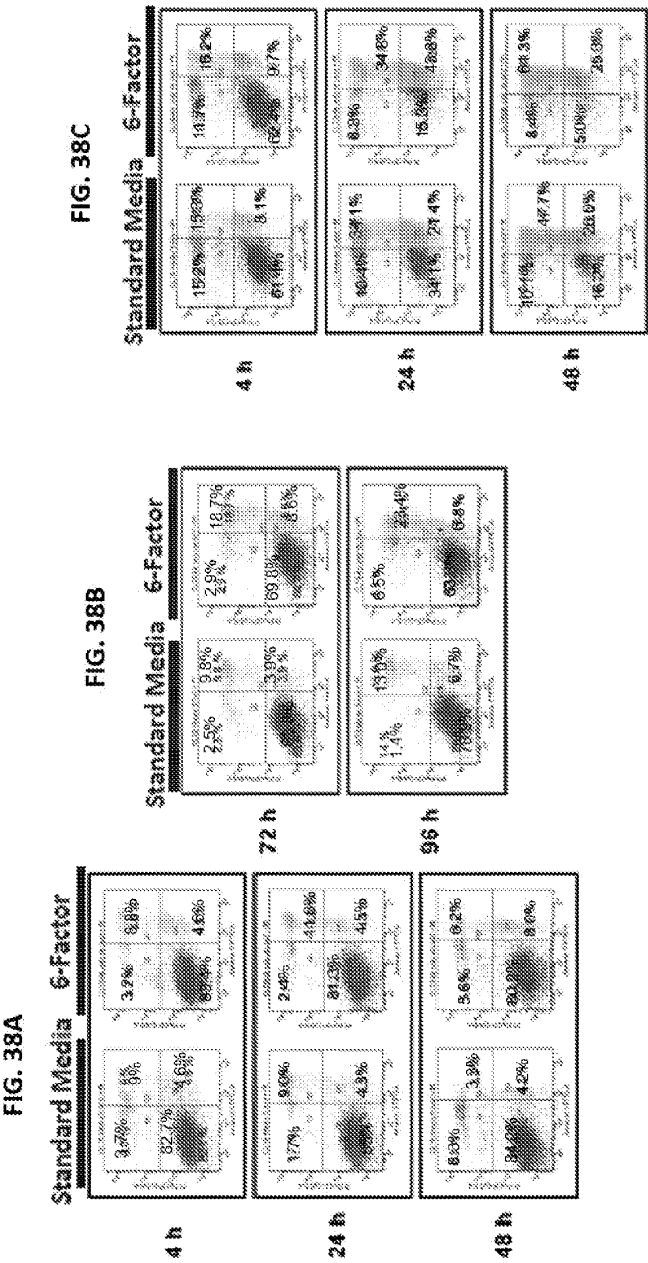
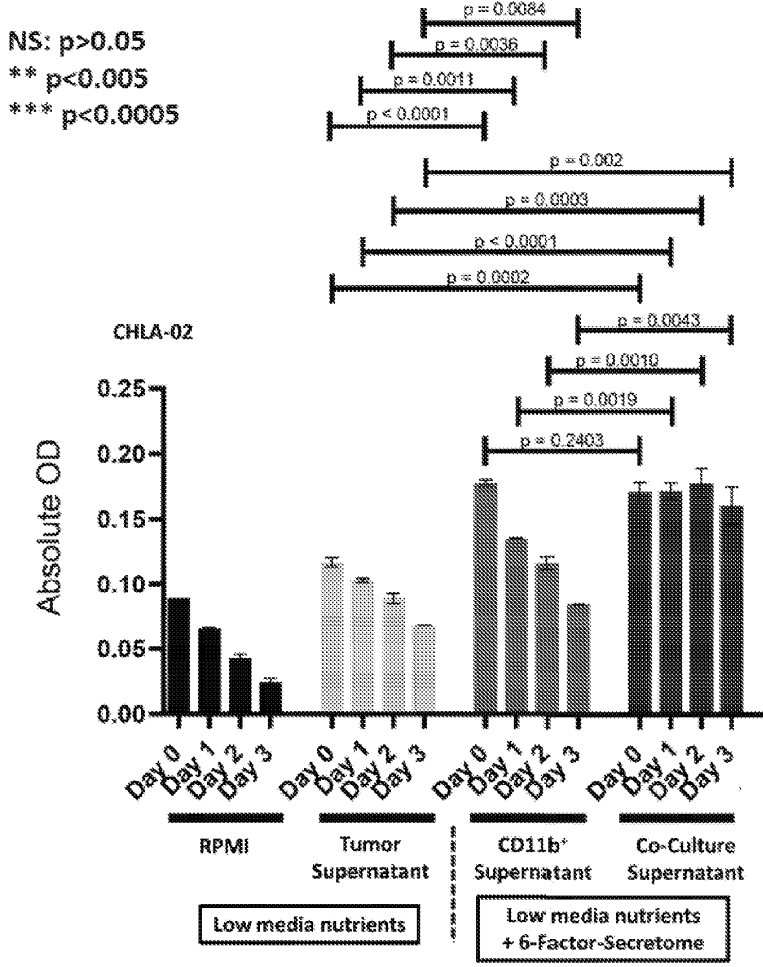


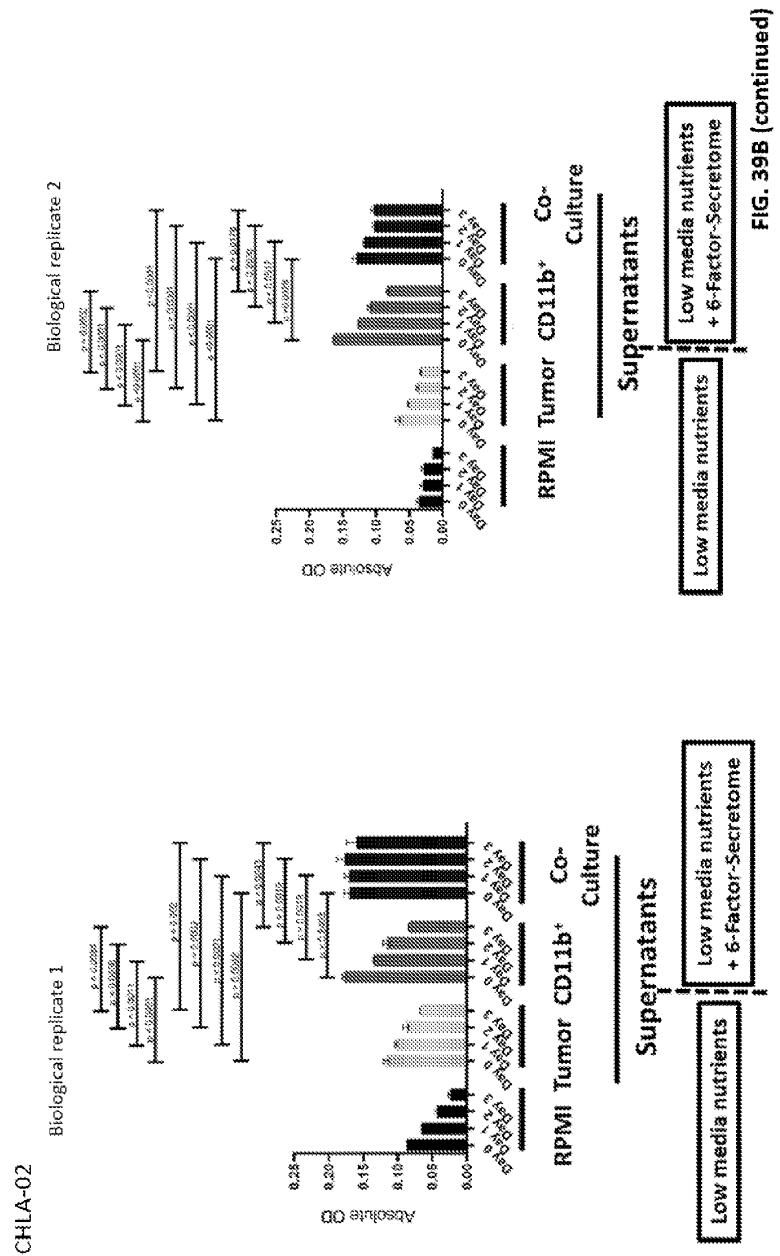
FIG. 38C  
(continued)











CHLA-02  
Biological replicate 3

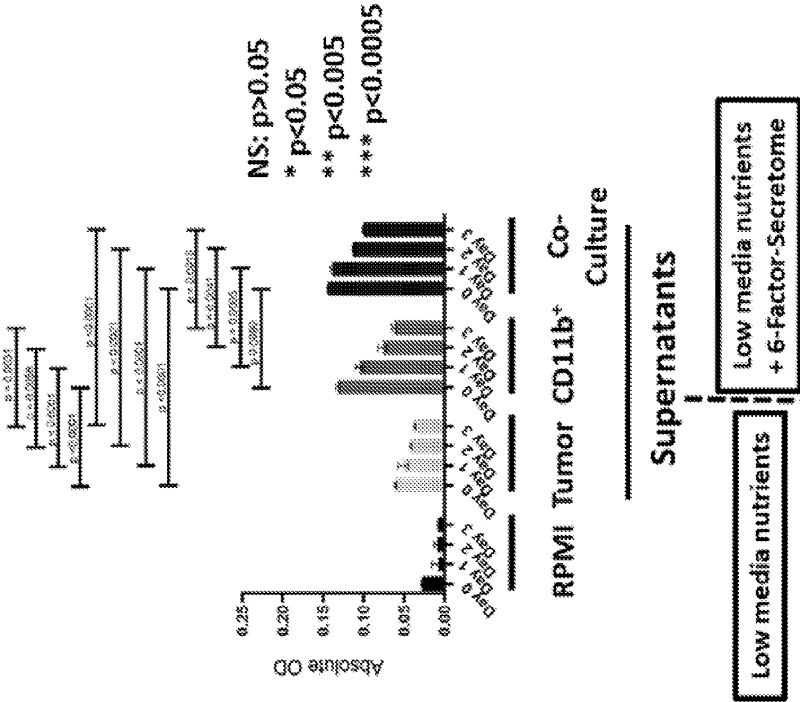


FIG. 39B (continued)

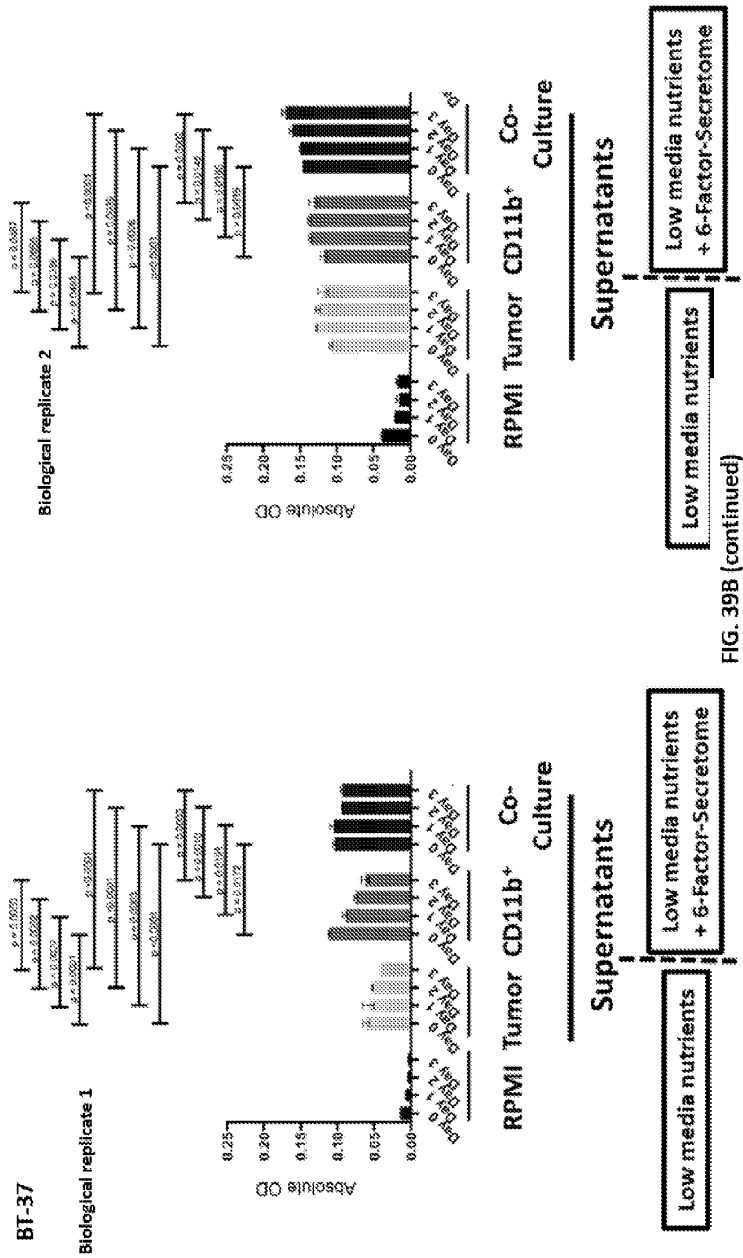
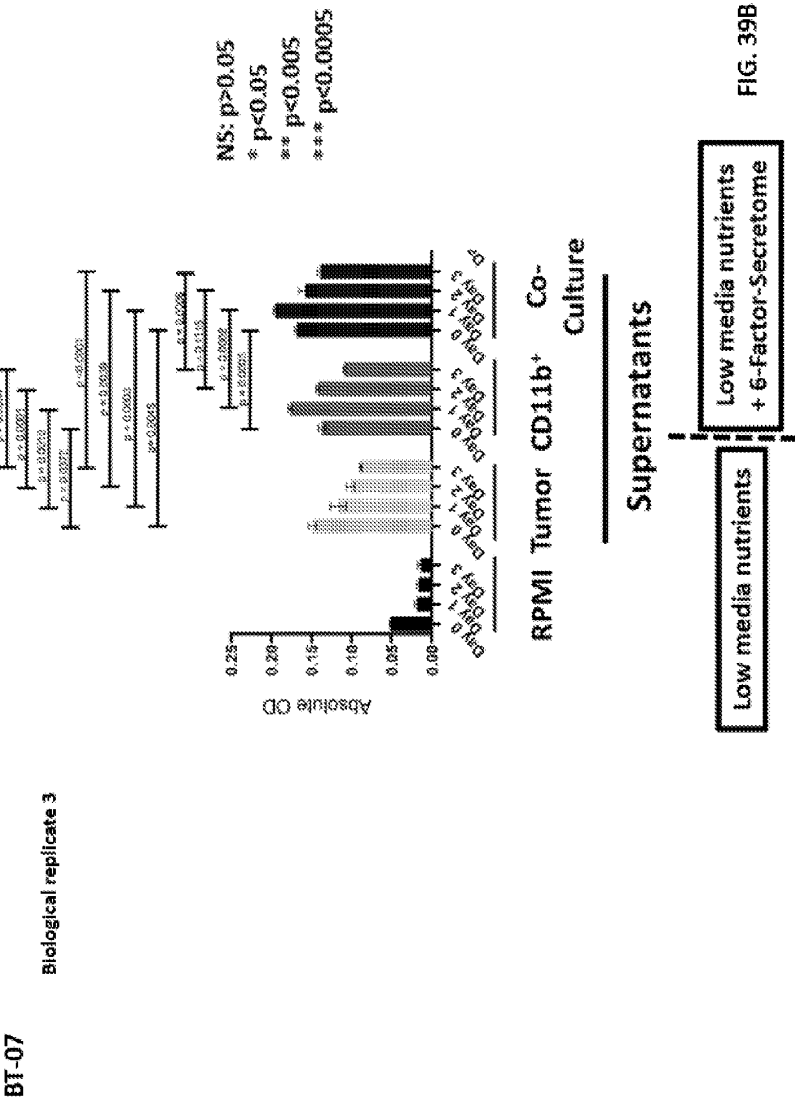


FIG. 39B (continued)



CHLA-02

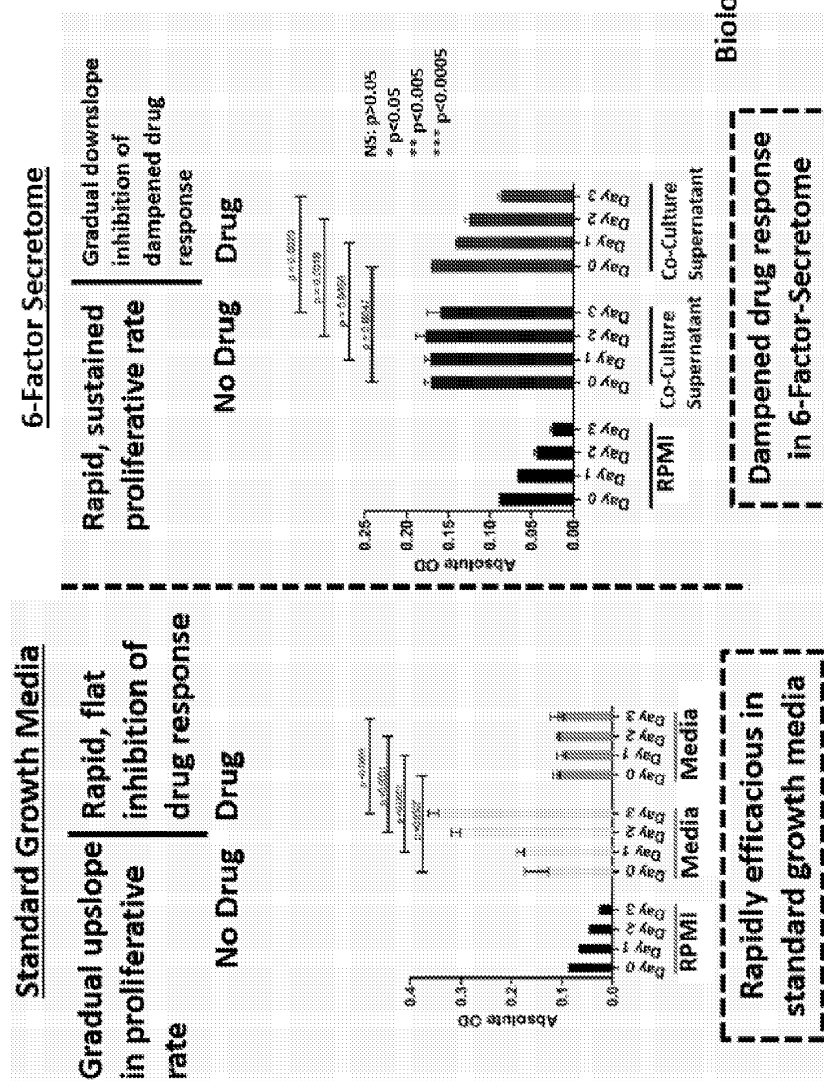
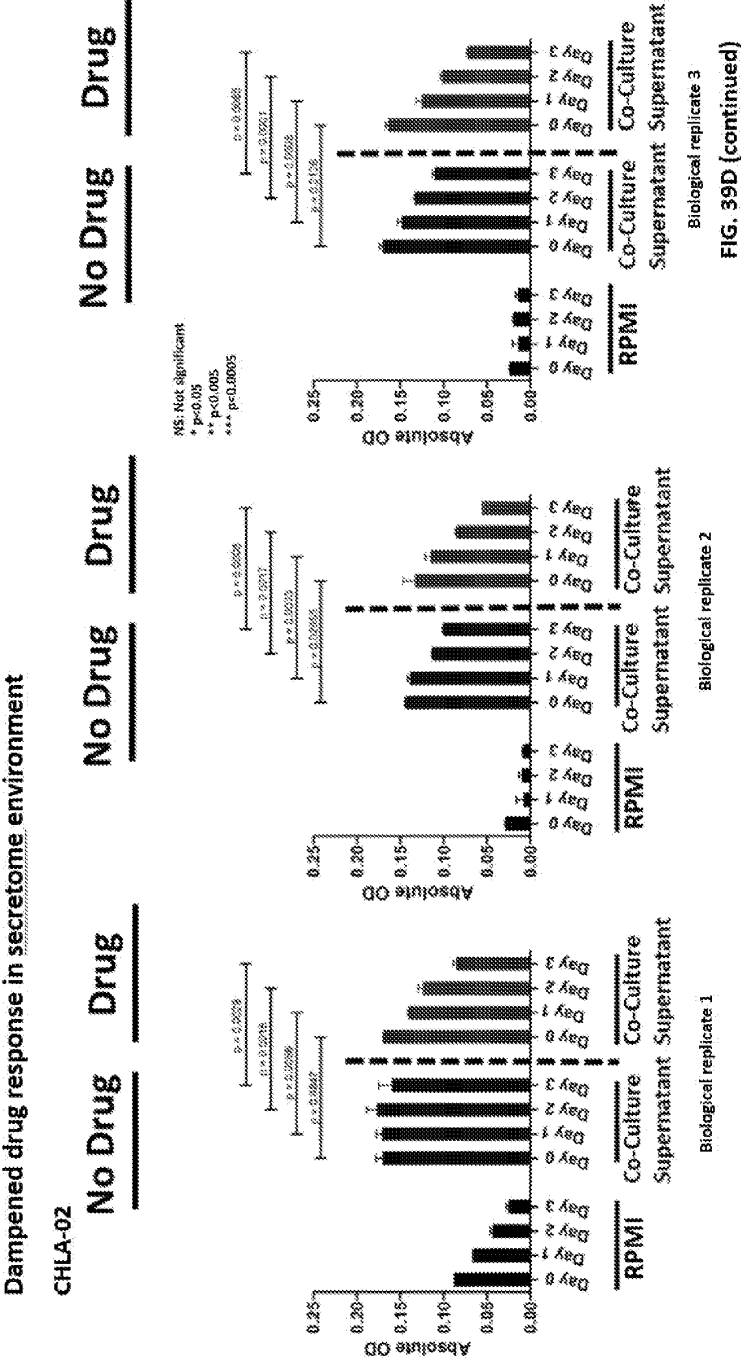
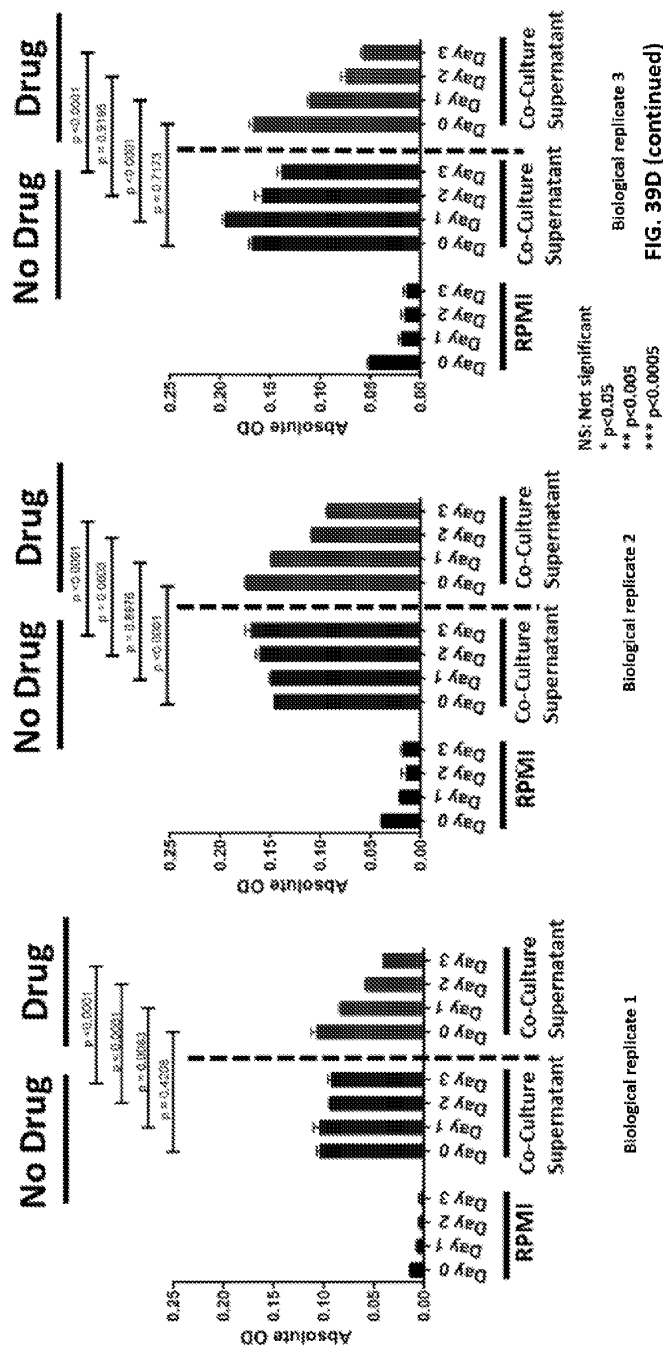
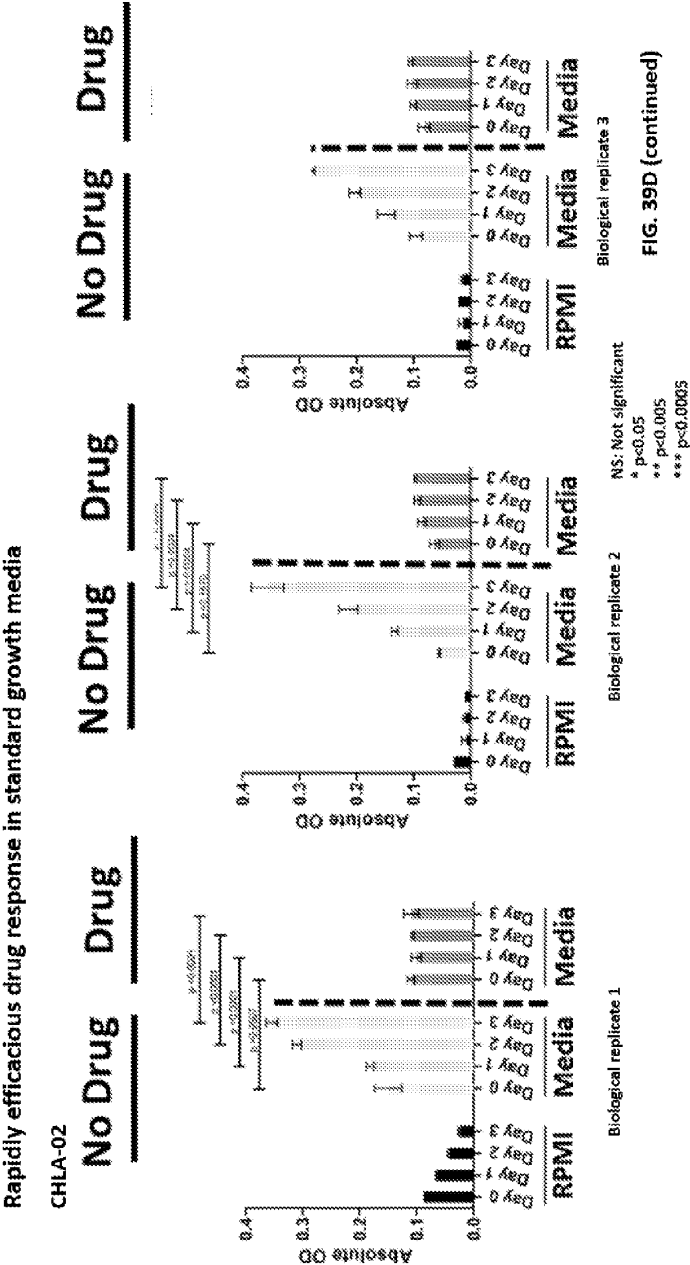


FIG. 39C

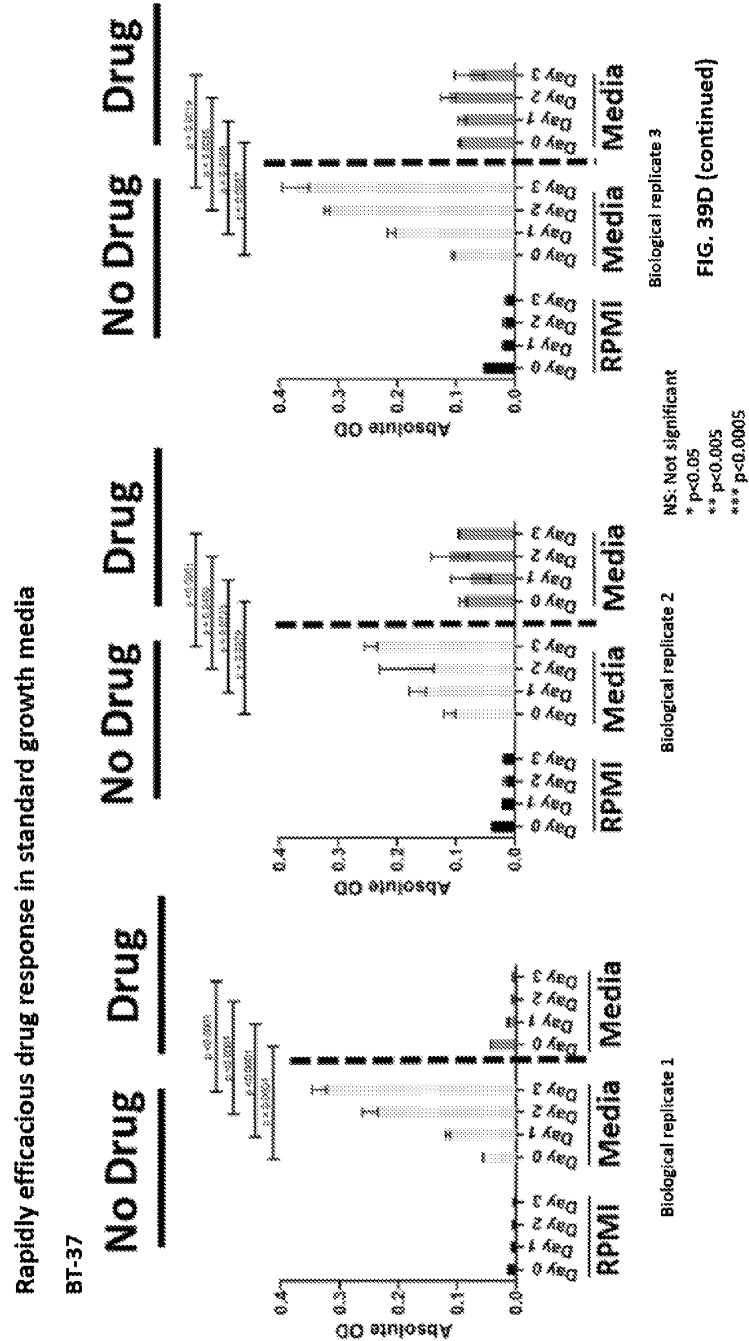


BT-37









Efficacy of drug is decreased in secretome, compared to standard growth media

CHLA-02 – Stem cell media

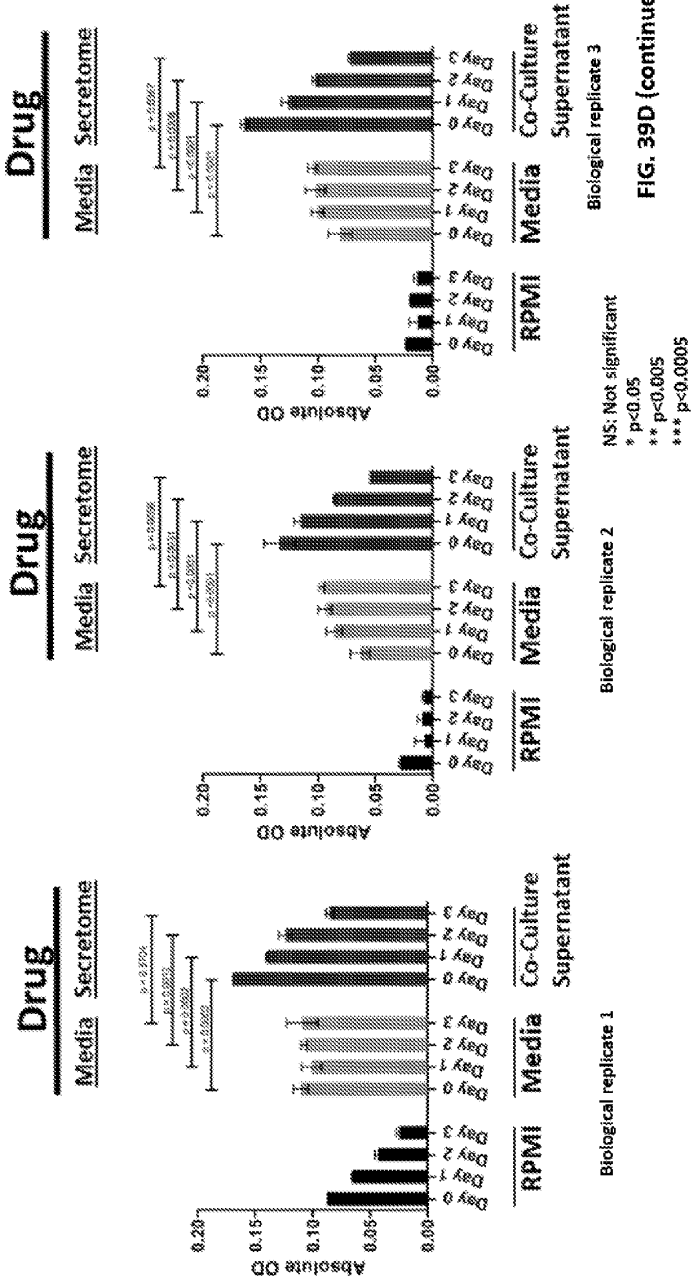
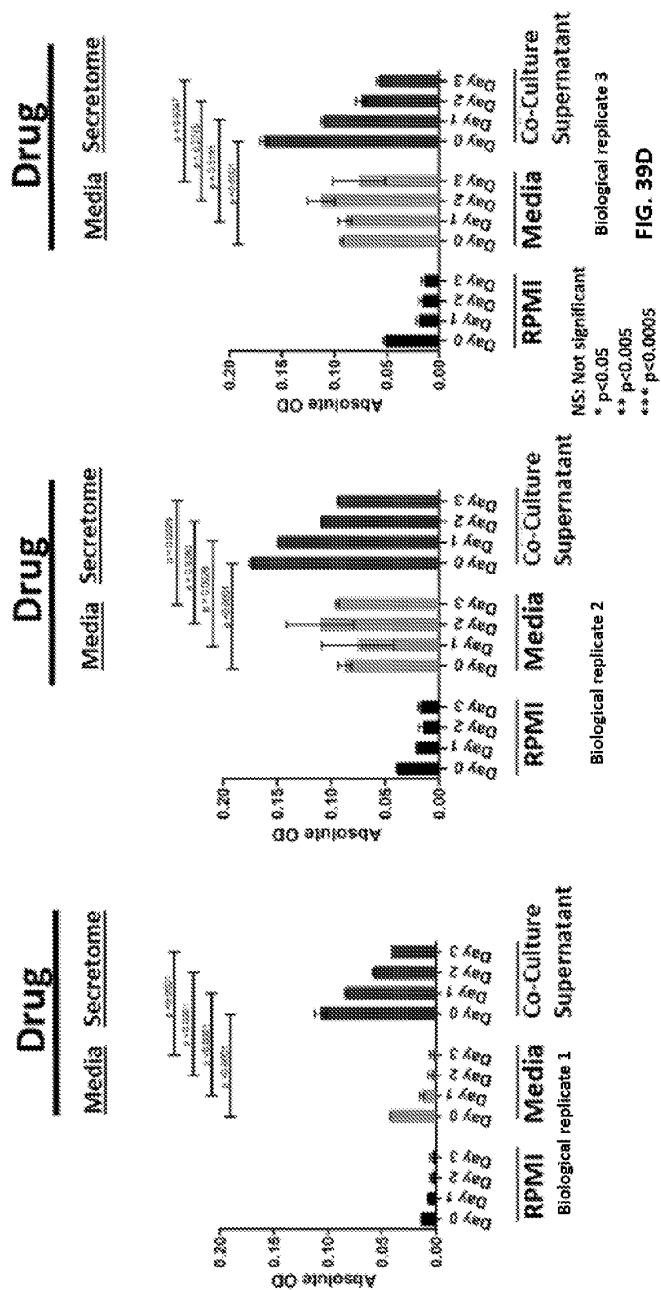


FIG. 39D (continued)

### BT-37 – Serum based growth media



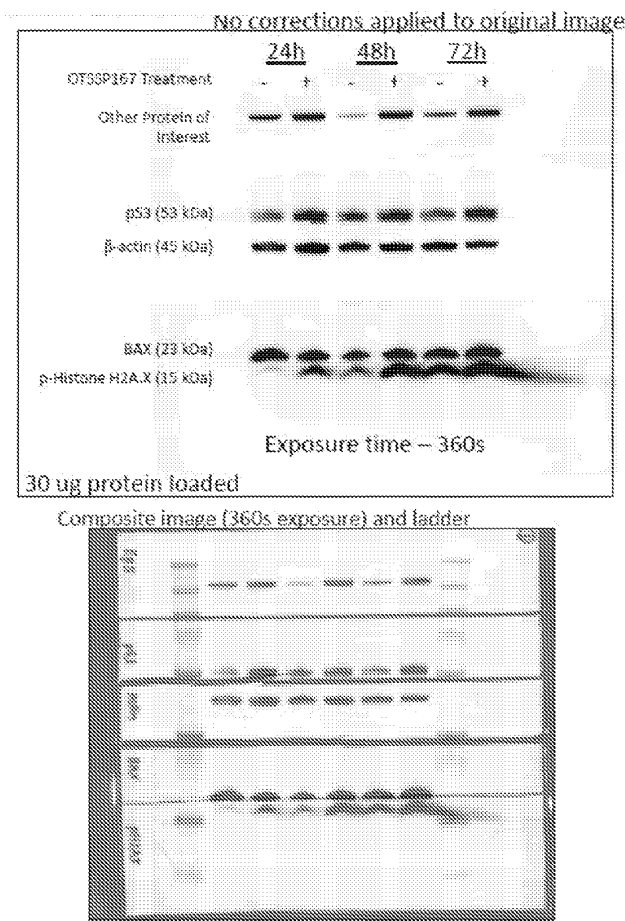


FIG. 40A

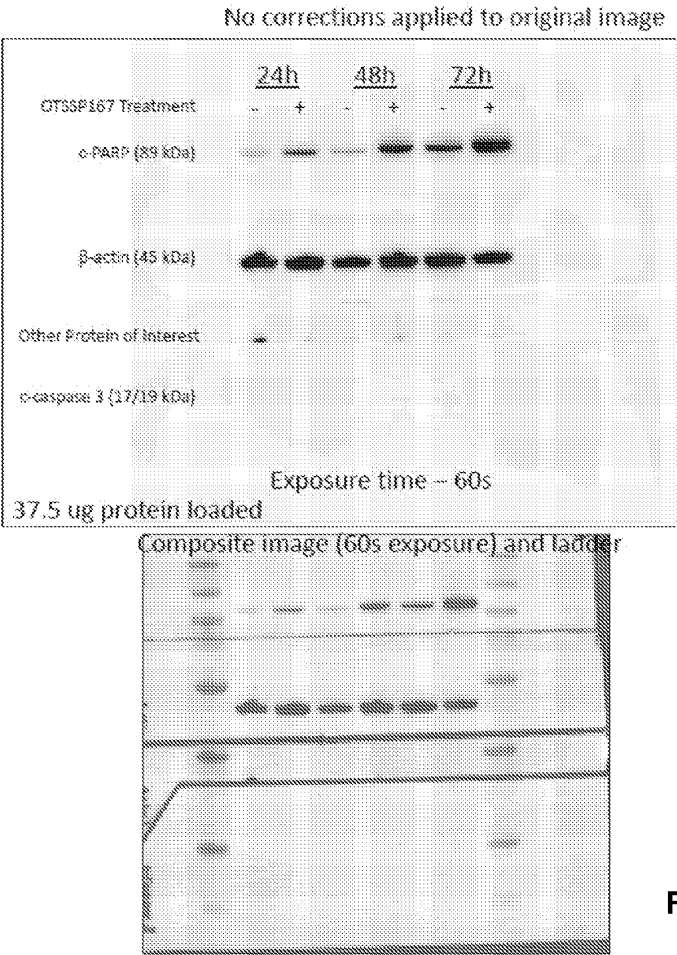


FIG. 40B

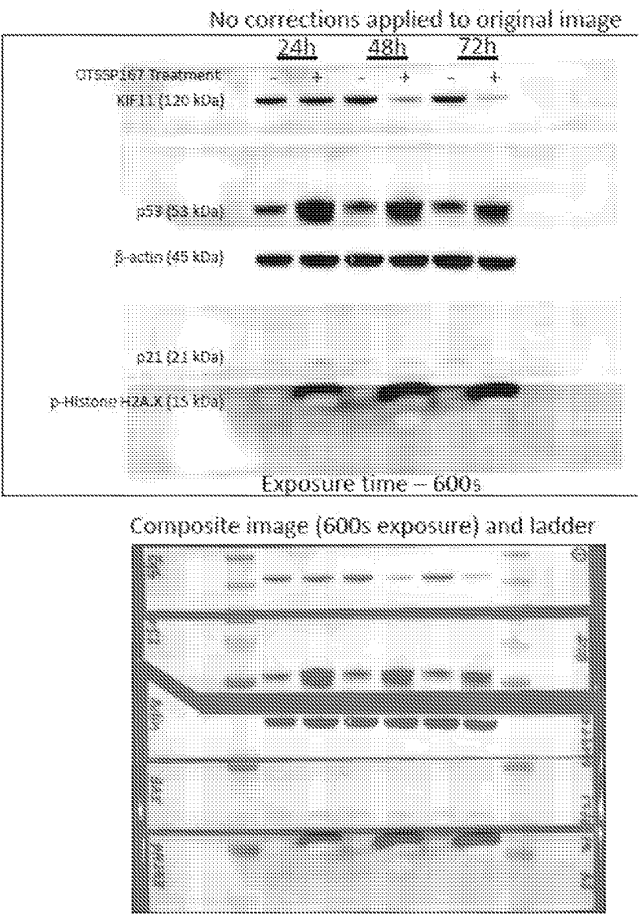


FIG. 40C

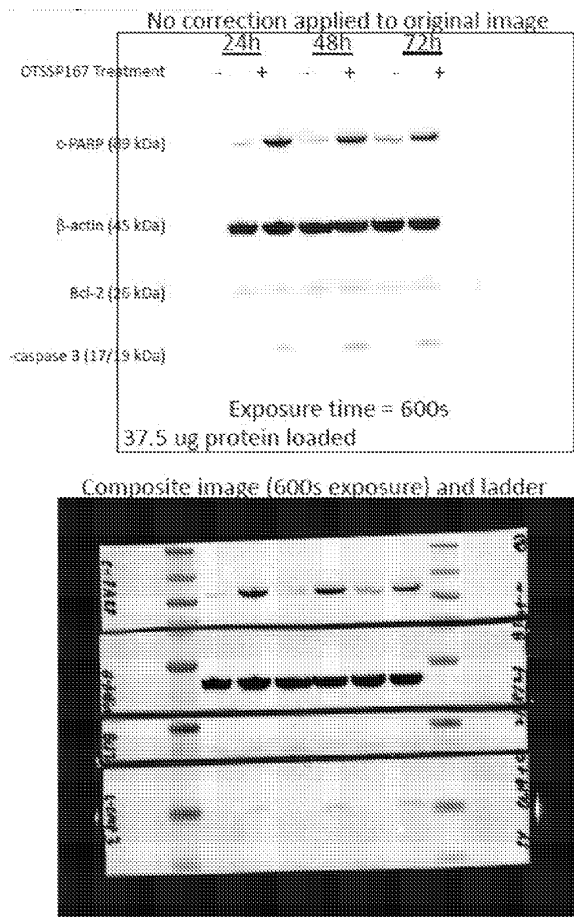


FIG. 40D

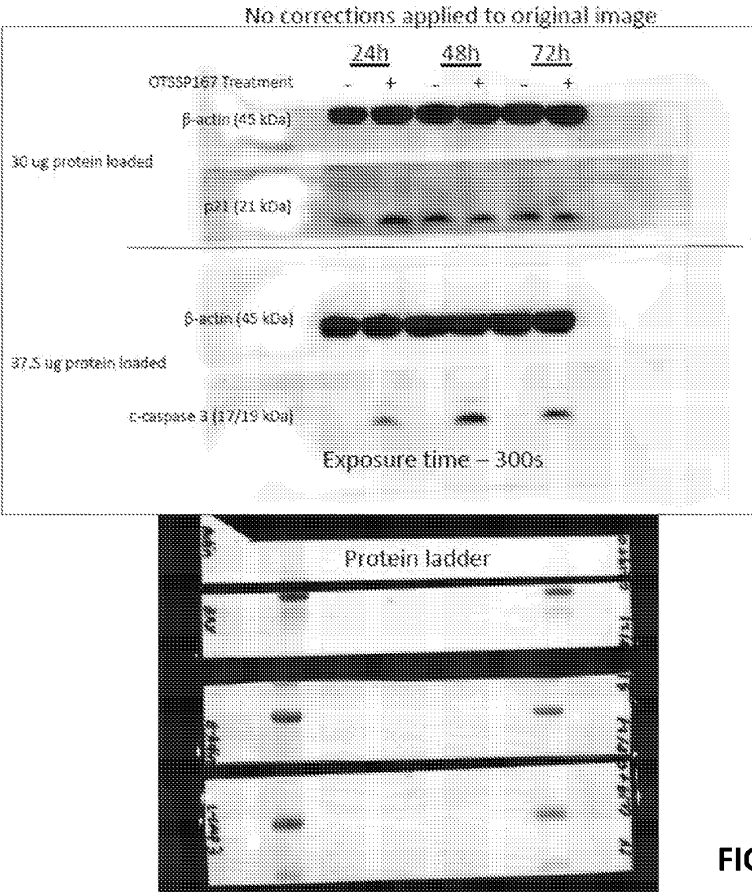
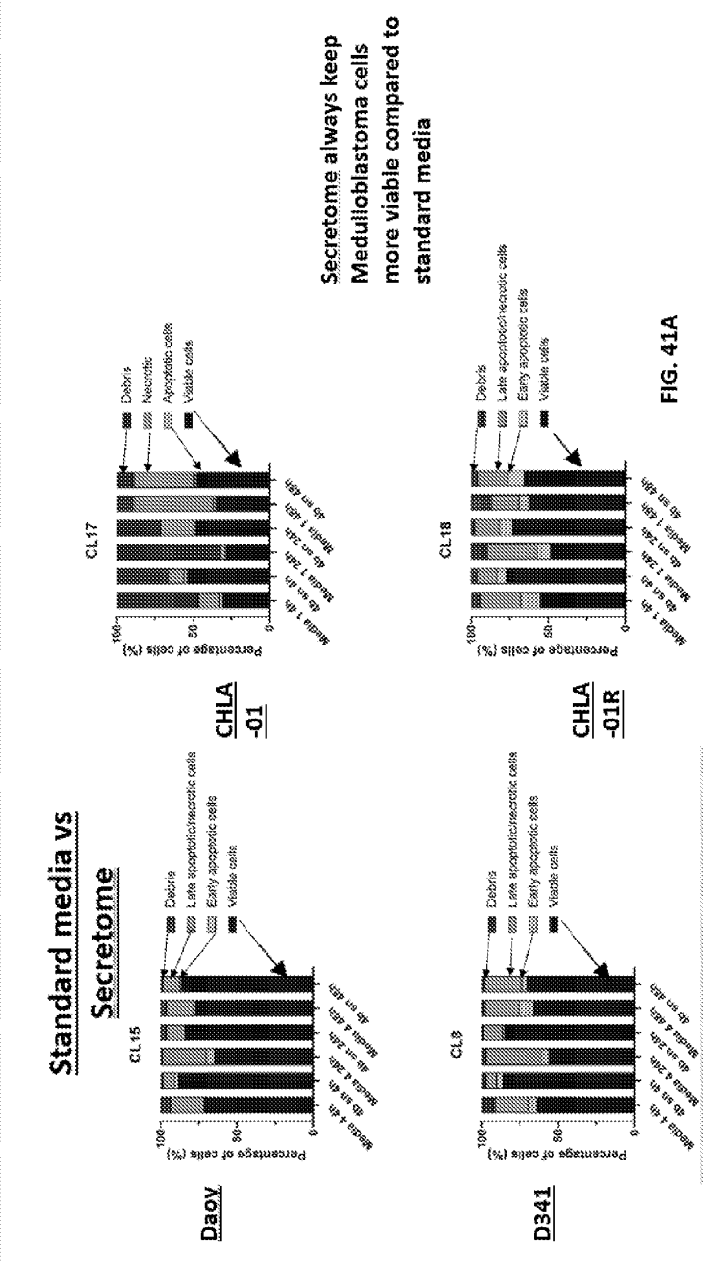
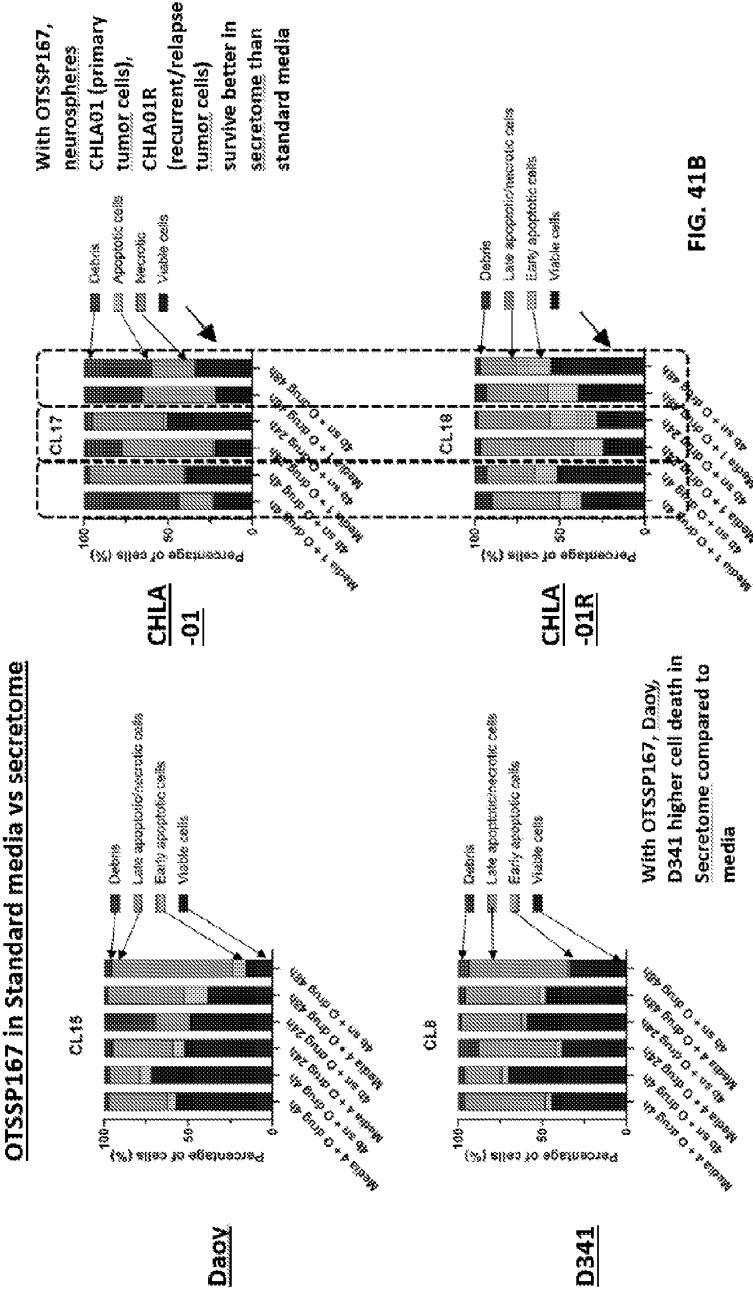
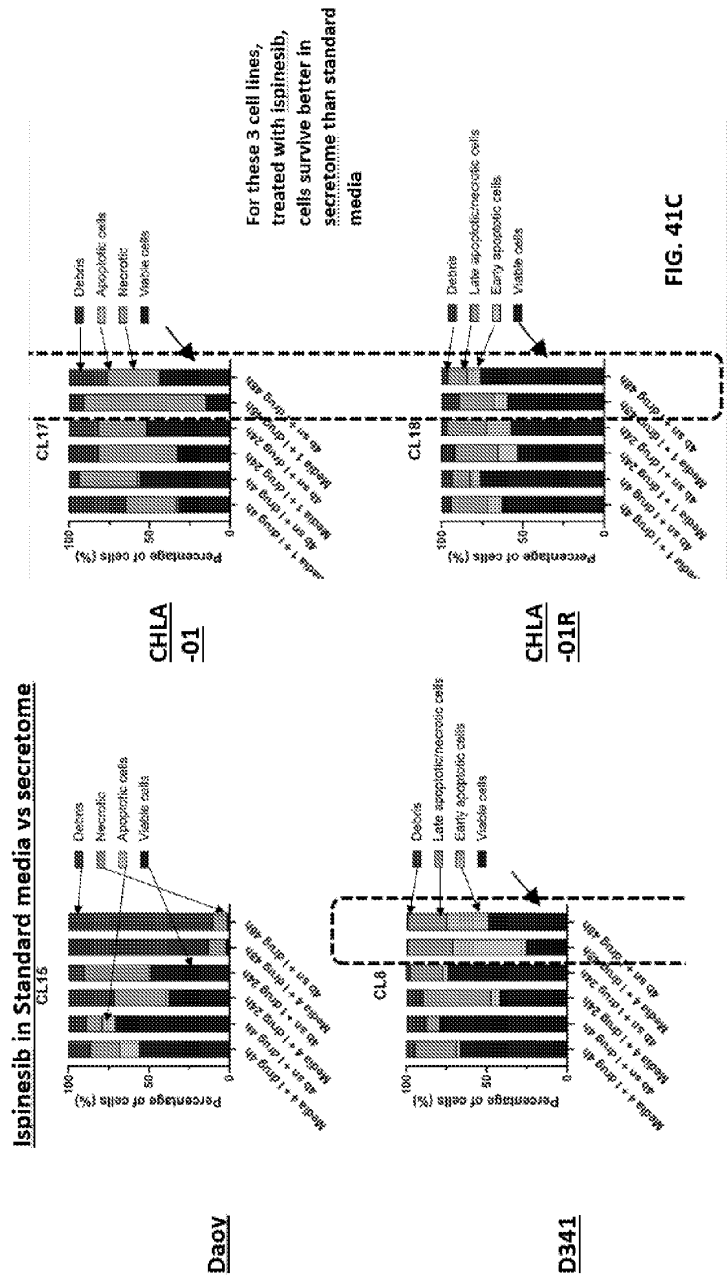


FIG. 40E









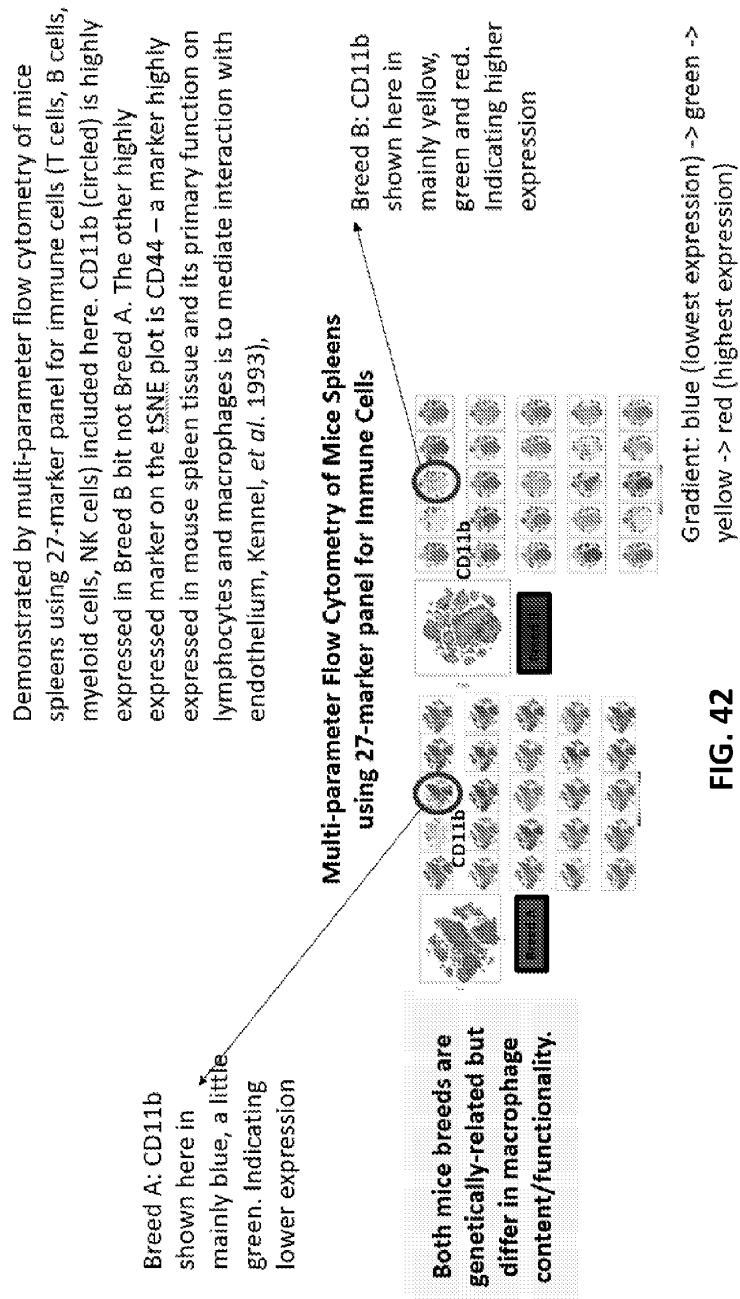
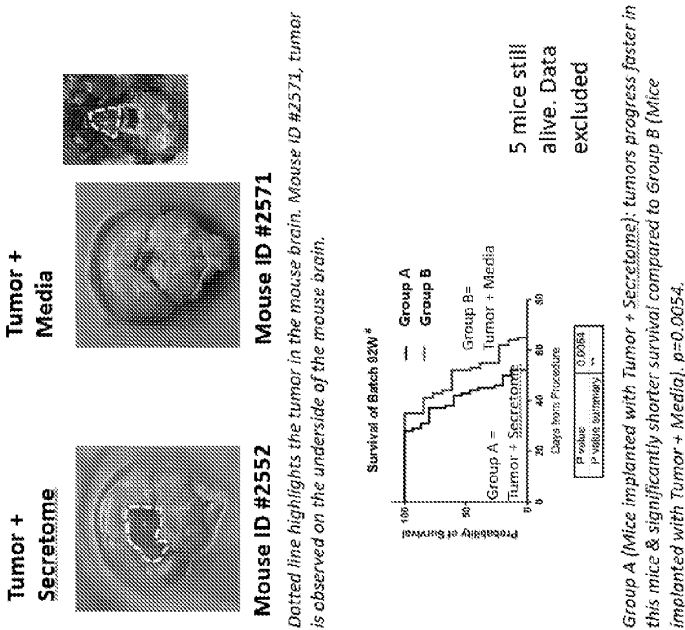


FIG. 42



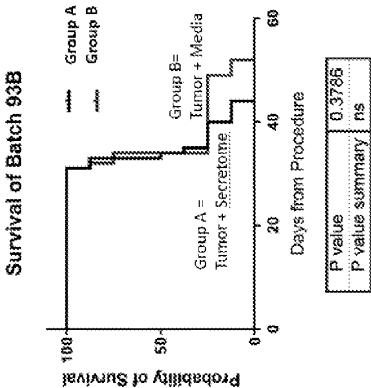
Brain Tumor Type 2: Medulloblastoma

Batch 94B

**In vivo Data.** Patient-derived orthotopic xenograft brain tumor model. Total 21 mice all injected with Tumor + Secretome. All in 1 experimental setting. 10 mice are in Control Group (no drug treatment). 11 mice are injected with Ispinesib (intraperitoneal injections). Mice are staged for disease using the staging criteria we previously established (Elghetany, Teo, Scientific Reports 2021).

|                                 | Tumor + Secretome Control Group (no Drug) (n=10) | Tumor + Secretome + Ispinesib Group (n=11) |
|---------------------------------|--------------------------------------------------|--------------------------------------------|
| Dead + Sick (Stage 2 and above) | 10 (100%)                                        | 2 (18.2%)                                  |
| Healthy                         | 0 (0%)                                           | 9 (81.8%)                                  |

In this same specific molecular subtype of medulloblastoma as Batch 93B, another batch of 21 mice were implanted with Tumor + Secretome in 1 experimental setting. All 21 mice successfully formed brain tumor. We have previously shown that Ispinesib is an effective drug for Medulloblastoma (Elghetany, Teo, Scientific Reports 2021). Data here shows that Ispinesib is also effective in PDX brain tumors implanted using secretome + Tumor.

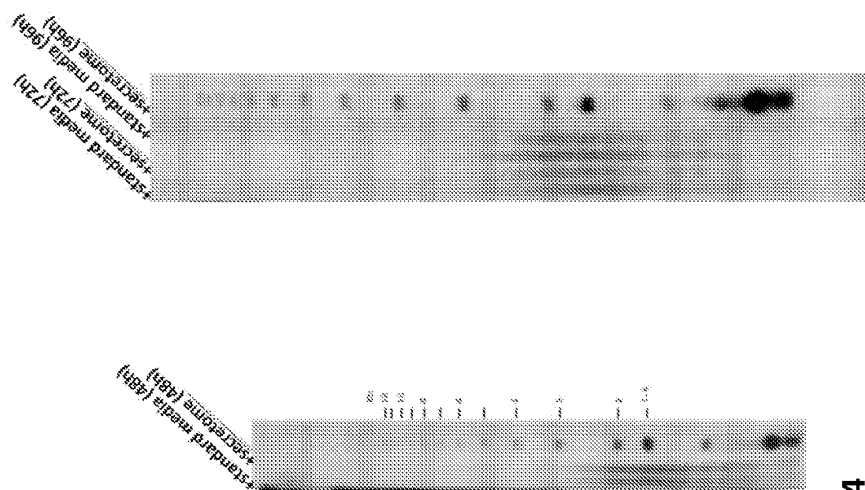


In this specific molecular subtype of medulloblastoma, there is no statistical difference in survival between Group A (Mice implanted with Tumor + Secretome) and Group B (Mice implanted with Tumor + Media).  $p=0.3786$ . Although mice with Tumor+ Secretome tend to progress faster.

FIG. 43B

CHLA-02

Southern Blot: Teleblot showing Telomere Length maintained in secretome, comparable to standard media. Effects long lasting to 96h.



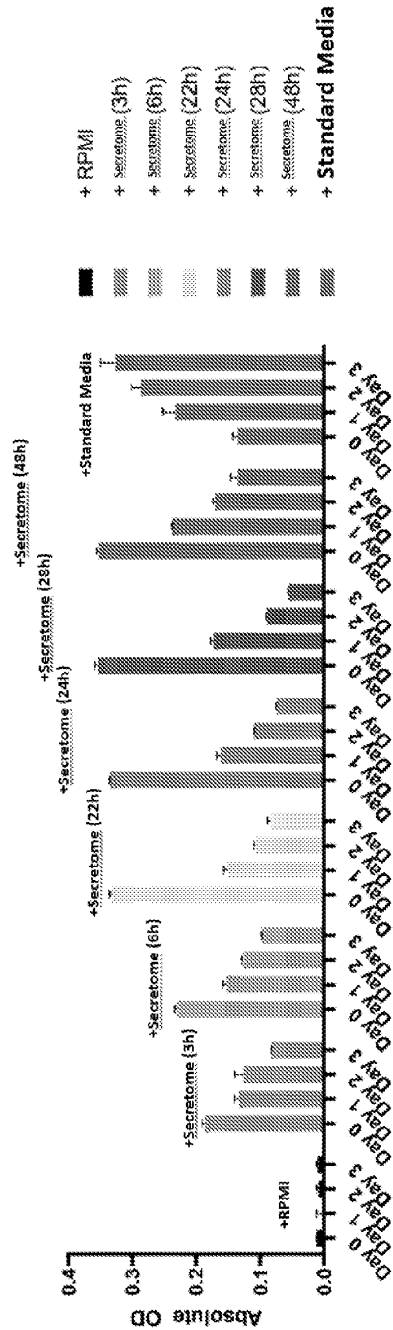


FIG. 45



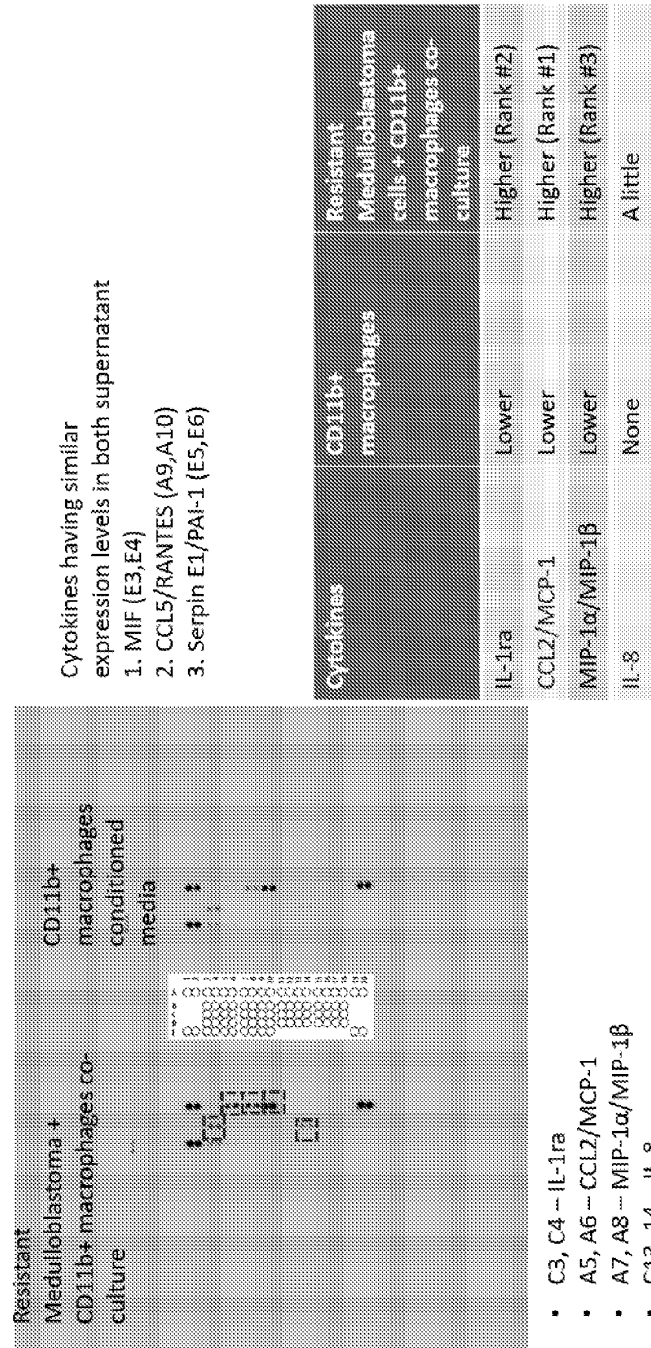


FIG. 46

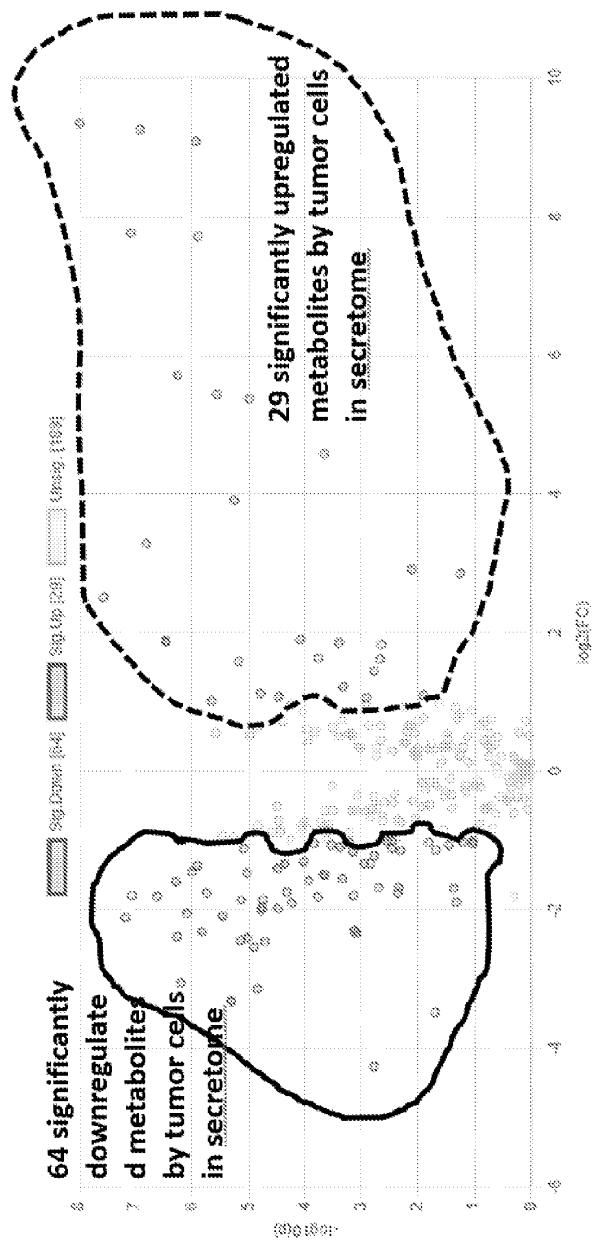
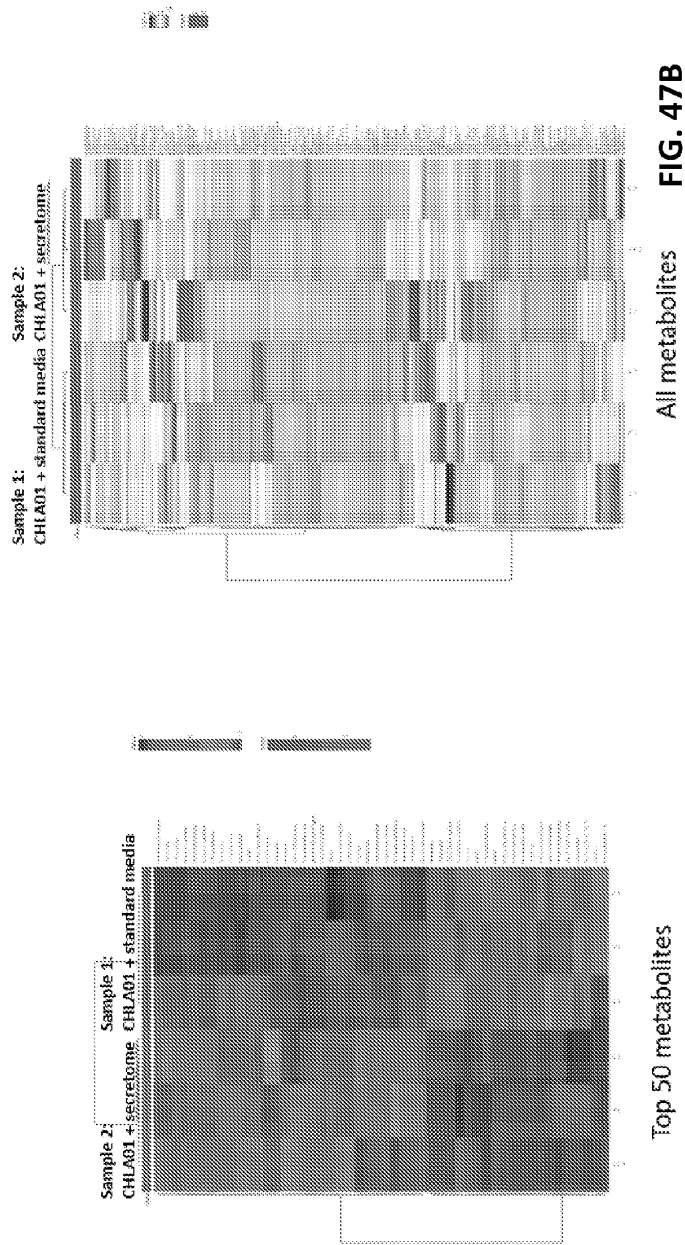
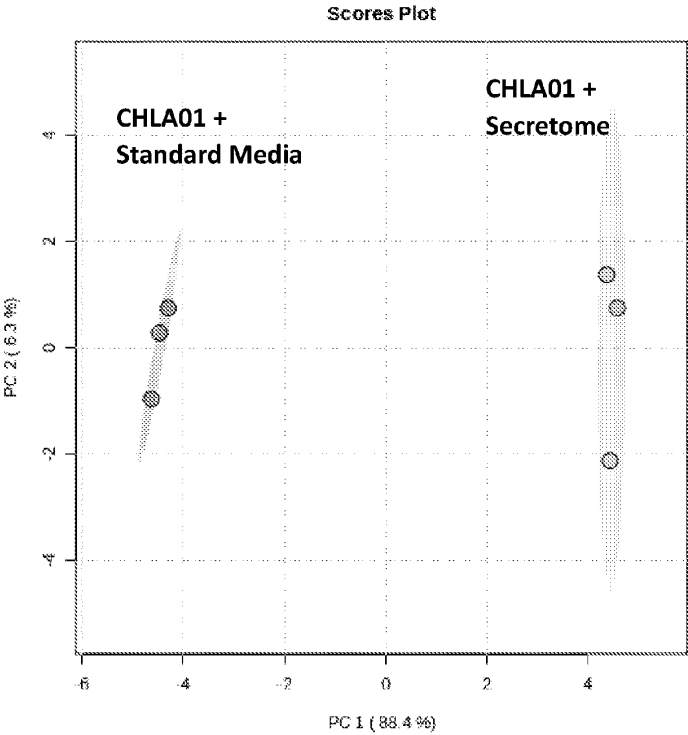


FIG. 47A





**FIG. 47C**





**FIG. 48B**

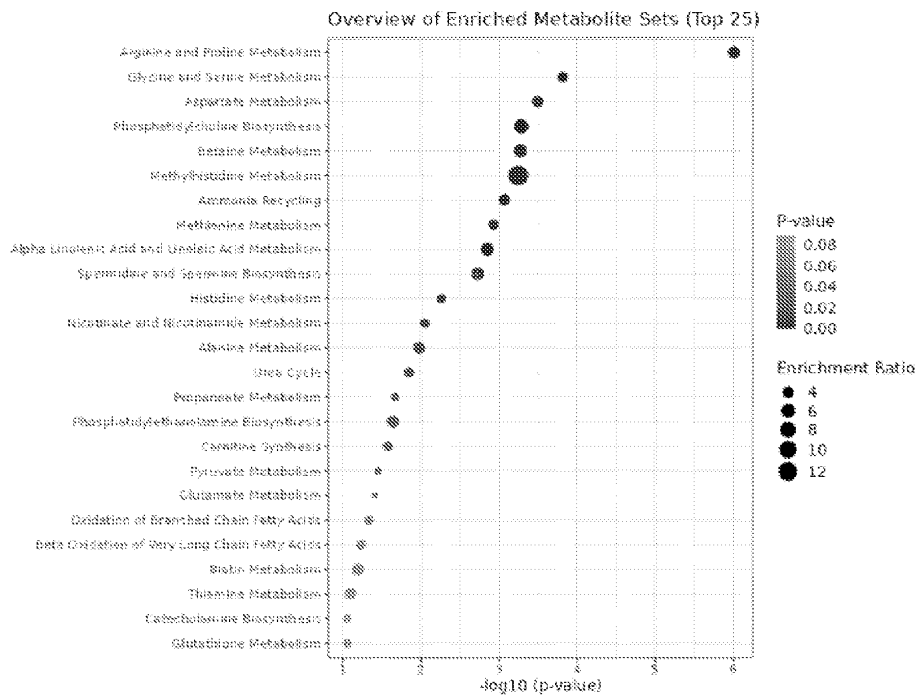


FIG. 48C

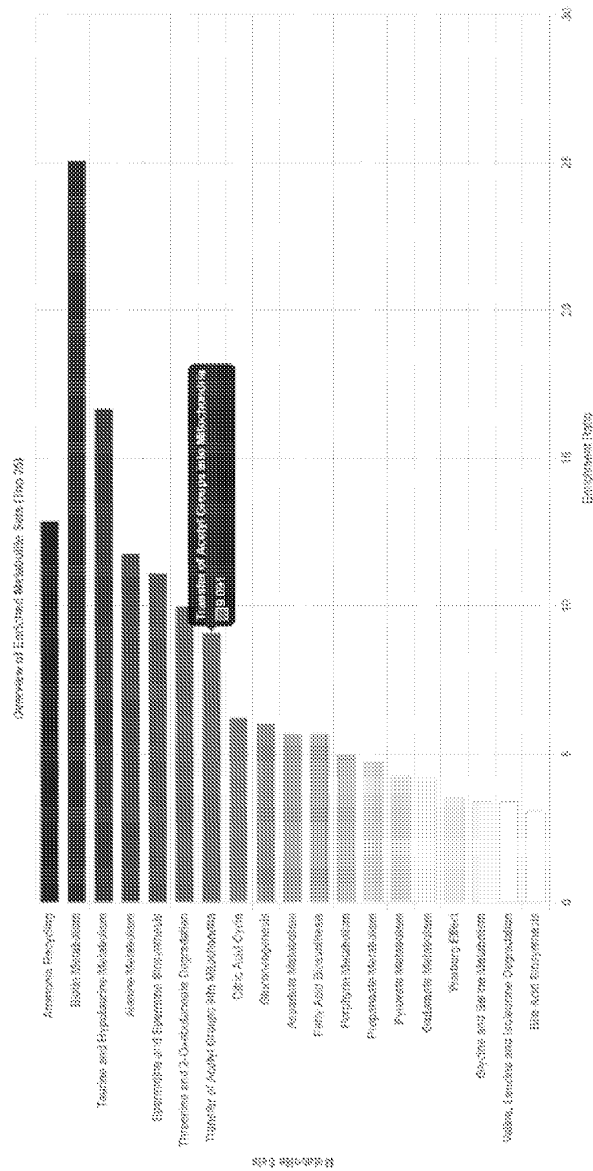
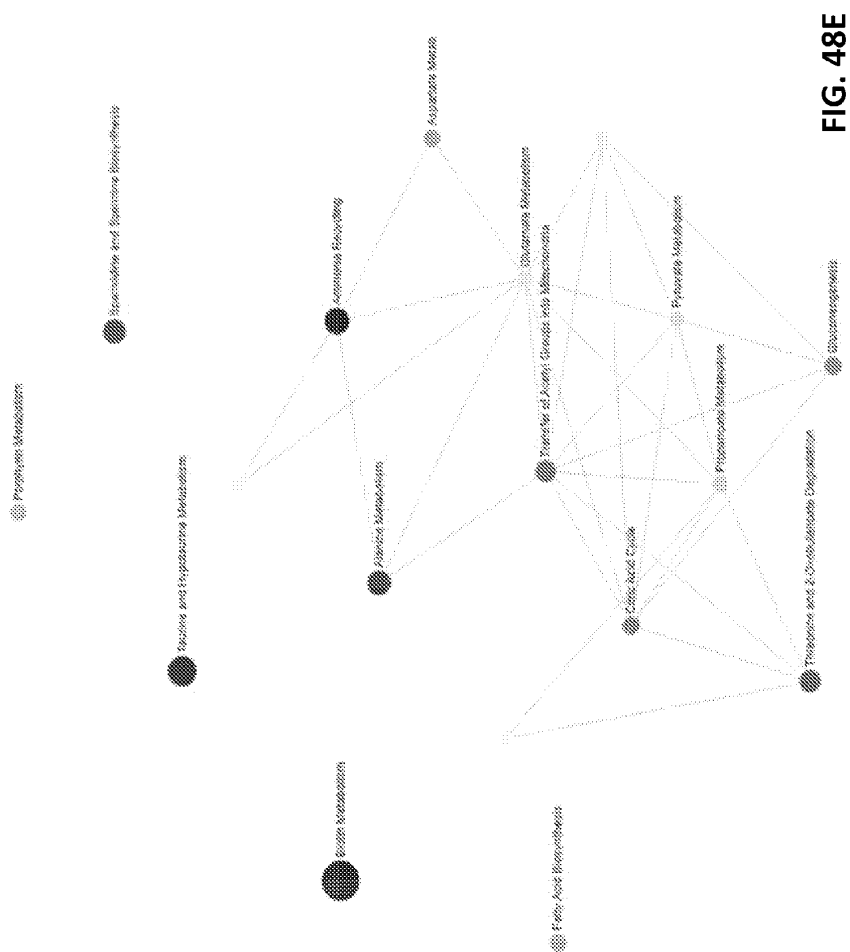


FIG. 48D





**FIG. 48E**

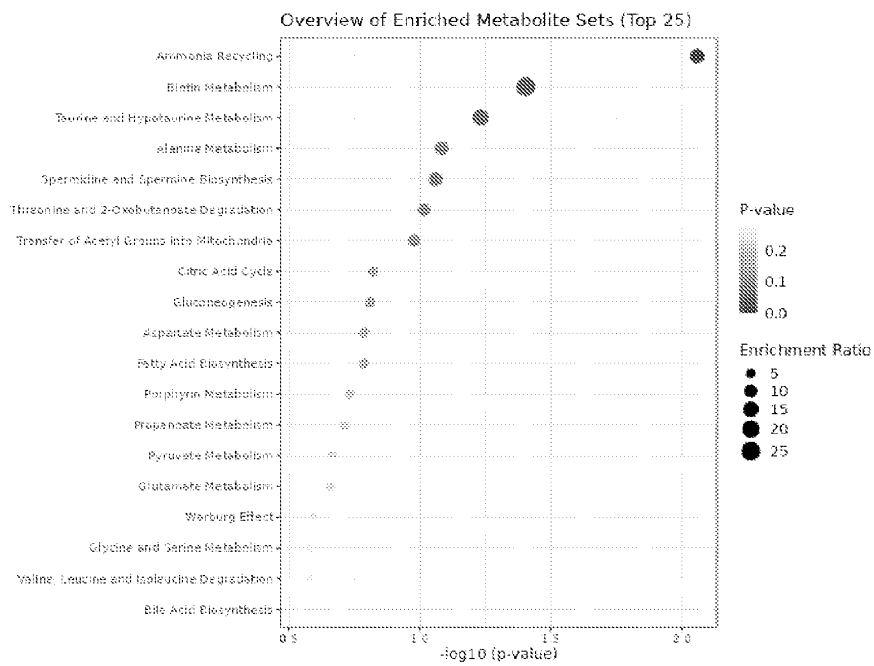
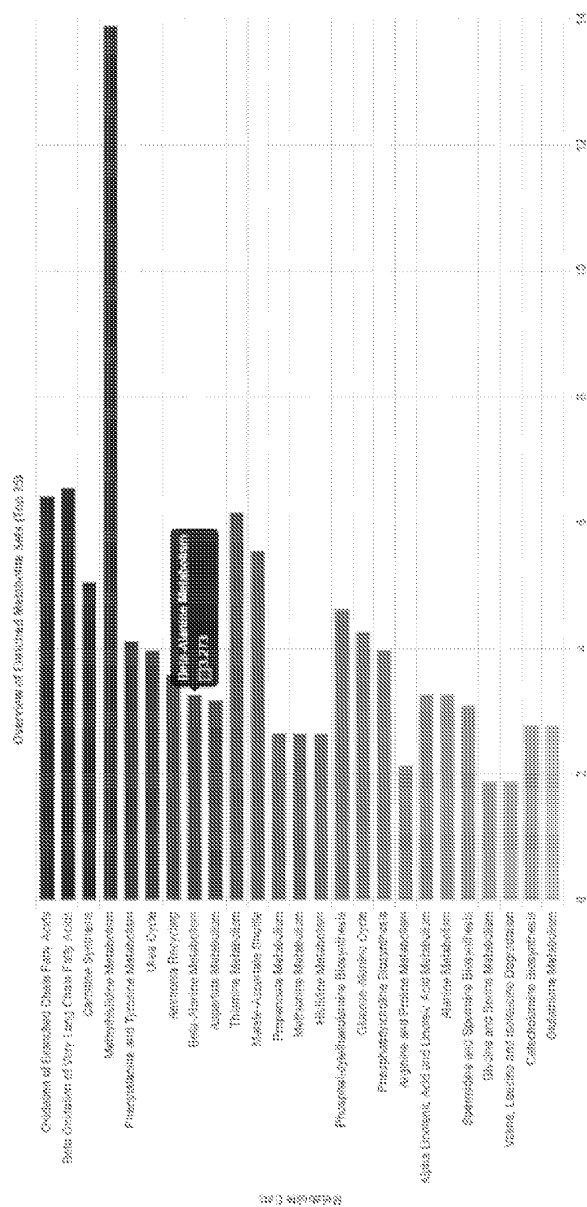


FIG. 48F



**FIG. 48G**



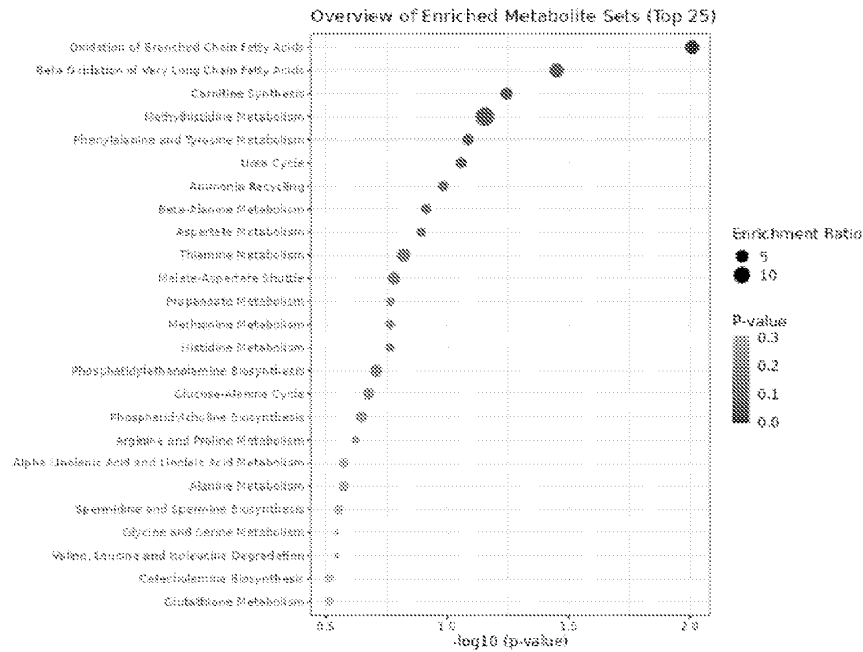


FIG. 48I

| Metabolic Set                                   | Yeast | Human | Espect | Proteome | Human P | FDK   | Results |
|-------------------------------------------------|-------|-------|--------|----------|---------|-------|---------|
| Utilization of Branched Chain Fatty Acids       | 26    | 1     | 0.467  | 0.00672  | 0.999   | 0.999 | Weak    |
| Beta Oxidation of Very Long Chain Fatty Acids   | 17    | 0     | 0.085  | 0.0034   | 1.0     | 1.0   | Weak    |
| Cardione Synthesis                              | 32    | 2     | 0.099  | 0.0003   | 1.0     | 1.0   | Weak    |
| Methylglutamate Metabolism                      | 4     | 1     | 0.0712 | 0.027    | 1.0     | 1.0   | Weak    |
| Phenylalanine and Tyrosine Interconversion      | 27    | 2     | 0.485  | 0.00021  | 1.0     | 1.0   | Weak    |
| Urea Cycle                                      | 28    | 2     | 0.593  | 0.00021  | 1.0     | 1.0   | Weak    |
| Acetamide Recycling                             | 13    | 0     | 0.557  | 0.0034   | 1.0     | 1.0   | Weak    |
| Peroxisomal Metabolism                          | 34    | 2     | 0.011  | 0.002    | 1.0     | 1.0   | Weak    |
| Aspartate Metabolism                            | 35    | 2     | 0.003  | 0.0005   | 1.0     | 1.0   | Weak    |
| Tyrosine Metabolism                             | 9     | 1     | 0.160  | 0.0031   | 1.0     | 1.0   | Weak    |
| Malic-Aspartate Shuttle                         | 33    | 1     | 0.18   | 0.0005   | 1.0     | 1.0   | Weak    |
| Ferrocyanide Metabolism                         | 40    | 1     | 0.754  | 0.002    | 1.0     | 1.0   | Weak    |
| Methionine Metabolism                           | 40    | 1     | 0.754  | 0.002    | 1.0     | 1.0   | Weak    |
| Mitochondrial Metabolism                        | 42    | 2     | 0.754  | 0.002    | 1.0     | 1.0   | Weak    |
| Citrate/Malate/Tetrahydrofolate Interconversion | 32    | 1     | 0.713  | 0.0005   | 1.0     | 1.0   | Weak    |
| Glutamate-Alanine Cycle                         | 32    | 1     | 0.234  | 0.0011   | 1.0     | 1.0   | Weak    |
| Phenylalanine/Tyrosine Interconversion          | 54    | 3     | 0.051  | 0.0005   | 1.0     | 1.0   | Weak    |
| Arginine and Proline Metabolism                 | 52    | 2     | 0.034  | 0.0005   | 1.0     | 1.0   | Weak    |
| Alpha-ketoglutarate and Lysine Metabolism       | 17    | 1     | 0.005  | 0.0005   | 1.0     | 1.0   | Weak    |
| Alanine Metabolism                              | 17    | 1     | 0.005  | 0.0005   | 1.0     | 1.0   | Weak    |

FIG. 48J (continued)

|                                                           |    |   |       |       |     |     |      |
|-----------------------------------------------------------|----|---|-------|-------|-----|-----|------|
| Urethane and Sulfone Compounds                            | 18 | 1 | 0.002 | 0.00  | 1.0 | 1.0 | View |
| Alkyl and Ester Metabolites                               | 56 | 2 | 1.00  | 0.000 | 1.0 | 1.0 | View |
| Alkyl, Urethane and Sulfone Degradation                   | 58 | 2 | 1.00  | 0.000 | 1.0 | 1.0 | View |
| Carbamate Breakdown                                       | 60 | 1 | 0.000 | 0.000 | 1.0 | 1.0 | View |
| Carbamate Metabolites                                     | 62 | 1 | 0.000 | 0.000 | 1.0 | 1.0 | View |
| Thiourethane and Carbamate Degradation                    | 64 | 1 | 0.000 | 0.000 | 1.0 | 1.0 | View |
| Benzoic Metabolites                                       | 21 | 1 | 0.000 | 0.000 | 1.0 | 1.0 | View |
| Amino Acid Metabolites                                    | 87 | 2 | 1.0   | 0.000 | 1.0 | 1.0 | View |
| Tyrosine Metabolites                                      | 70 | 2 | 1.00  | 0.000 | 1.0 | 1.0 | View |
| Glutamic Metabolites                                      | 26 | 1 | 0.000 | 0.00  | 1.0 | 1.0 | View |
| Urea Metabolites                                          | 13 | 2 | 1.00  | 0.000 | 1.0 | 1.0 | View |
| Benzoic Acid Metabolites                                  | 27 | 1 | 0.000 | 0.000 | 1.0 | 1.0 | View |
| Metabolites Ben-Cladon of Ben-Cladon Saturated Ben-Cladon | 27 | 1 | 0.000 | 0.000 | 1.0 | 1.0 | View |
| Metabolites Ben-Cladon of Long Chain Saturated Ben-Cladon | 28 | 1 | 0.000 | 0.000 | 1.0 | 1.0 | View |
| Urea Metabolites                                          | 89 | 1 | 0.000 | 0.000 | 1.0 | 1.0 | View |
| Urea Degradation                                          | 90 | 1 | 0.000 | 0.000 | 1.0 | 1.0 | View |
| Benzoic Sulfon Metabolites                                | 92 | 1 | 0.000 | 0.000 | 1.0 | 1.0 | View |
| Benzoic and Benzoic Degradation                           | 96 | 1 | 0.000 | 0.000 | 1.0 | 1.0 | View |
| Phenylglycid Metabolites                                  | 40 | 1 | 0.000 | 0.000 | 1.0 | 1.0 | View |
| Benzoic Metabolites                                       | 43 | 1 | 0.000 | 0.000 | 1.0 | 1.0 | View |
| Phenylglycid Metabolites                                  | 42 | 1 | 0.000 | 0.000 | 1.0 | 1.0 | View |
| Benzoic Metabolites                                       | 46 | 1 | 0.000 | 0.000 | 1.0 | 1.0 | View |
| Phenylglycid Metabolites                                  | 57 | 1 | 0.000 | 0.000 | 1.0 | 1.0 | View |
| Phenylglycid Metabolites                                  | 52 | 1 | 0.000 | 0.000 | 1.0 | 1.0 | View |
| Phenylglycid Metabolites                                  | 55 | 1 | 0.000 | 0.000 | 1.0 | 1.0 | View |

FIG. 48J

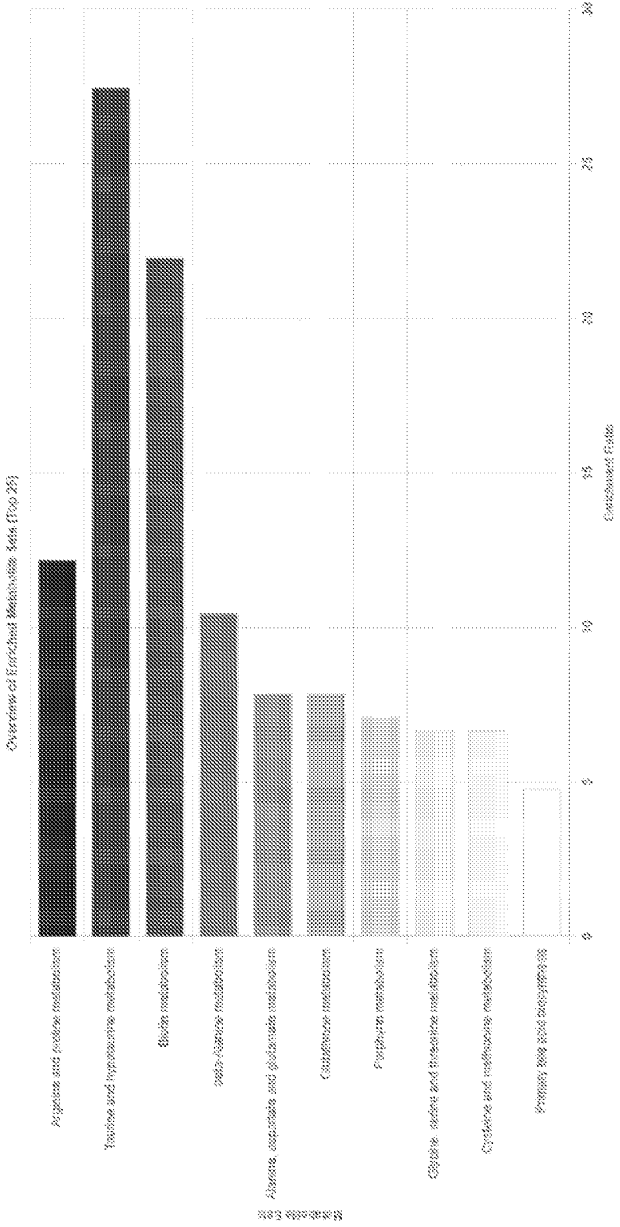


FIG. 49A



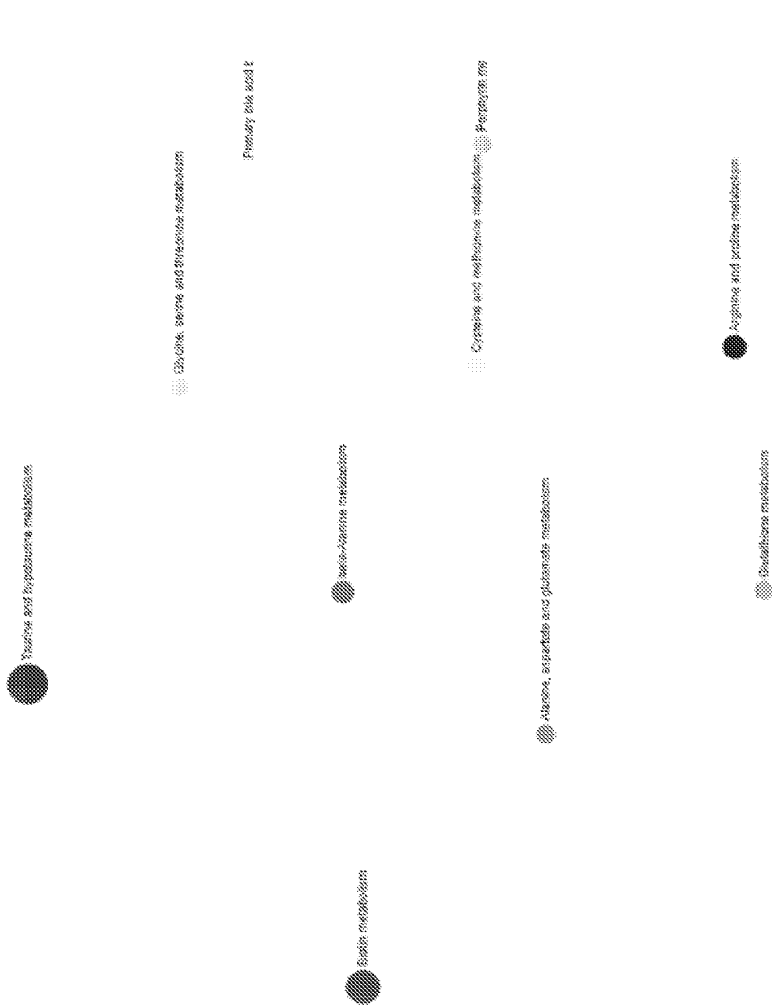


FIG. 49B

| Metabolic Set                               | Count | Hits | Expected | P-value | Median P | Q2%  | Detailed |
|---------------------------------------------|-------|------|----------|---------|----------|------|----------|
| Arginine and proline metabolism             | 36    | 2    | 0.164    | 0.0162  | 0.82     | 0.85 | View     |
| Taurine and hypotaurine metabolism          | 8     | 1    | 0.0184   | 0.0009  | 1.0      | 1.0  | View     |
| Sucrose metabolism                          | 10    | 1    | 0.0455   | 0.0447  | 1.0      | 1.0  | View     |
| beta-Alanine metabolism                     | 13    | 1    | 0.0055   | 0.0019  | 1.0      | 1.0  | View     |
| Alanine, aspartate and glutamate metabolism | 20    | 1    | 0.127    | 0.120   | 1.0      | 1.0  | View     |
| Glutathione metabolism                      | 28    | 1    | 0.137    | 0.101   | 1.0      | 1.0  | View     |
| Propanoic acid metabolism                   | 31    | 1    | 0.141    | 0.103   | 1.0      | 1.0  | View     |
| Glycine, serine and proline metabolism      | 30    | 1    | 0.15     | 0.141   | 1.0      | 1.0  | View     |
| Cysteine and methionine metabolism          | 33    | 1    | 0.15     | 0.141   | 1.0      | 1.0  | View     |
| Primary bile acid biosynthesis              | 48    | 1    | 0.209    | 0.192   | 1.0      | 1.0  | View     |

FIG. 49C

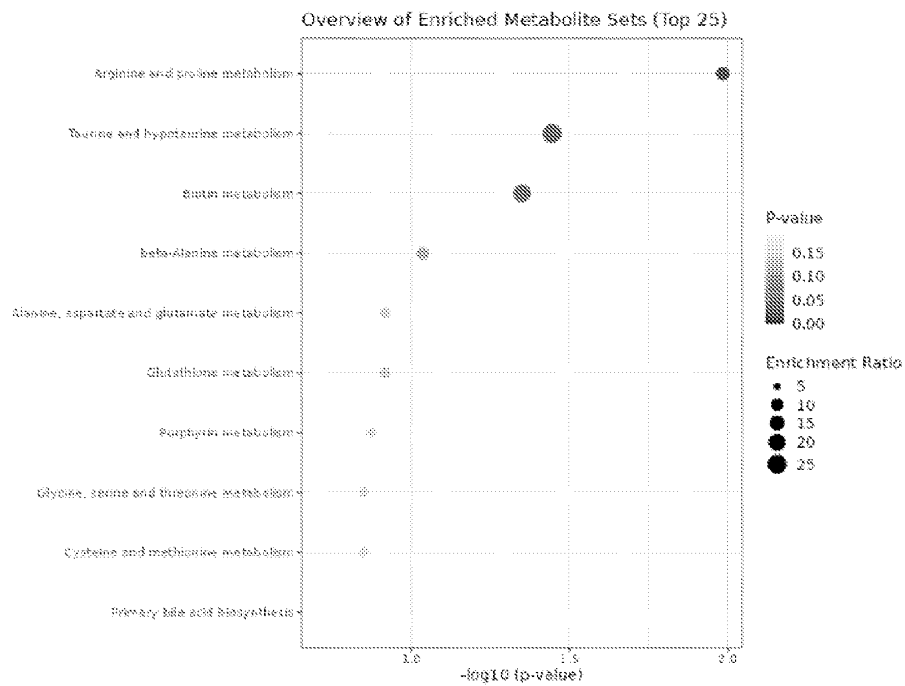


FIG. 49D

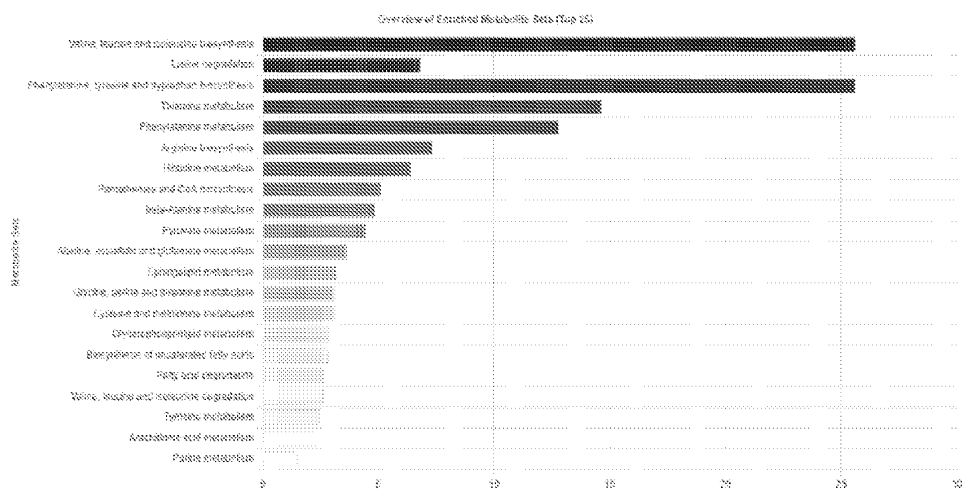


FIG. 49E

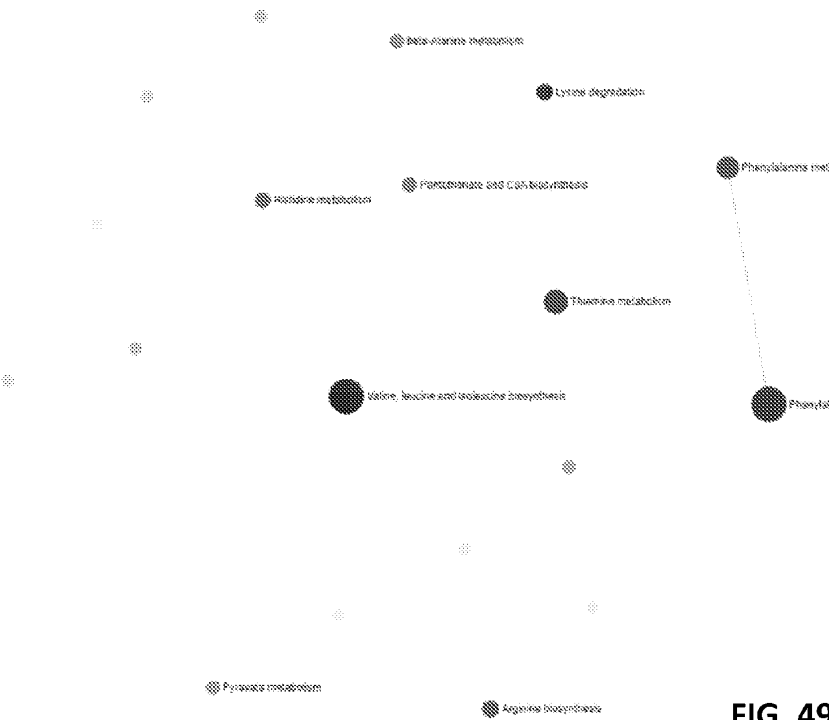


FIG. 49F

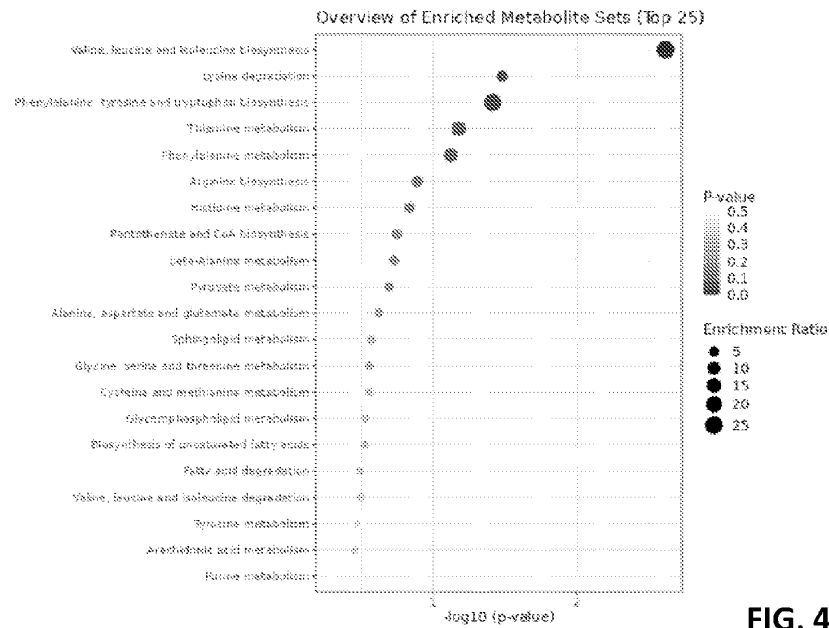


FIG. 49G

| Metabolic Set                                       | Total | Min | Expect | P-value | False P | FDR   | Details              |
|-----------------------------------------------------|-------|-----|--------|---------|---------|-------|----------------------|
| Valine, leucine and isoleucine metabolism           | 8     | 2   | 4.678  | 0.0024  | 0.167   | 0.192 | <a href="#">View</a> |
| Glycine degradation                                 | 20    | 2   | 0.252  | 0.002   | 1.0     | 1.0   | <a href="#">View</a> |
| Phenylalanine, tyrosine and tryptophan biosynthesis | 4     | 1   | 0.039  | 0.0005  | 0.0     | 1.0   | <a href="#">View</a> |
| Threonine metabolism                                | 7     | 1   | 0.0982 | 0.0602  | 1.0     | 1.0   | <a href="#">View</a> |
| Phenylalanine metabolism                            | 8     | 1   | 0.075  | 0.0759  | 1.0     | 1.0   | <a href="#">View</a> |
| Arginine biosynthesis                               | 14    | 1   | 0.189  | 0.109   | 1.0     | 1.0   | <a href="#">View</a> |
| Histidine metabolism                                | 10    | 1   | 0.104  | 0.145   | 1.0     | 1.0   | <a href="#">View</a> |
| Asparagine and Asn. biosynthesis                    | 20    | 1   | 0.095  | 0.179   | 0.0     | 1.0   | <a href="#">View</a> |
| Serine/threonine metabolism                         | 21    | 1   | 0.206  | 0.197   | 1.0     | 1.0   | <a href="#">View</a> |
| Pyruvate metabolism                                 | 33    | 1   | 0.034  | 0.288   | 0.0     | 1.0   | <a href="#">View</a> |
| Alanine, aspartate and glutamate metabolism         | 26    | 1   | 0.073  | 0.322   | 0.0     | 1.0   | <a href="#">View</a> |
| Sphingolipid metabolism                             | 50    | 1   | 0.312  | 0.271   | 0.0     | 1.0   | <a href="#">View</a> |
| Serine, threonine and tryptophan metabolism         | 34    | 1   | 0.022  | 0.279   | 1.0     | 1.0   | <a href="#">View</a> |
| Cysteine and methionine metabolism                  | 38    | 1   | 0.312  | 0.279   | 1.0     | 1.0   | <a href="#">View</a> |
| Glycerophospholipid metabolism                      | 36    | 1   | 0.051  | 0.3     | 0.0     | 1.0   | <a href="#">View</a> |
| Biosynthesis of unsaturated fatty acids             | 30    | 1   | 0.081  | 0.3     | 1.0     | 1.0   | <a href="#">View</a> |
| Fatty acid degradation                              | 59    | 1   | 0.38   | 0.321   | 0.0     | 1.0   | <a href="#">View</a> |
| Valine, leucine and isoleucine degradation          | 26    | 1   | 0.28   | 0.307   | 1.0     | 1.0   | <a href="#">View</a> |
| Tyrosine metabolism                                 | 40    | 1   | 0.409  | 0.341   | 1.0     | 1.0   | <a href="#">View</a> |
| Amino acid metabolism                               | 46    | 1   | 0.429  | 0.284   | 0.0     | 1.0   | <a href="#">View</a> |
| Purine metabolism                                   | 79    | 1   | 0.020  | 0.596   | 1.0     | 1.0   | <a href="#">View</a> |

FIG. 49H

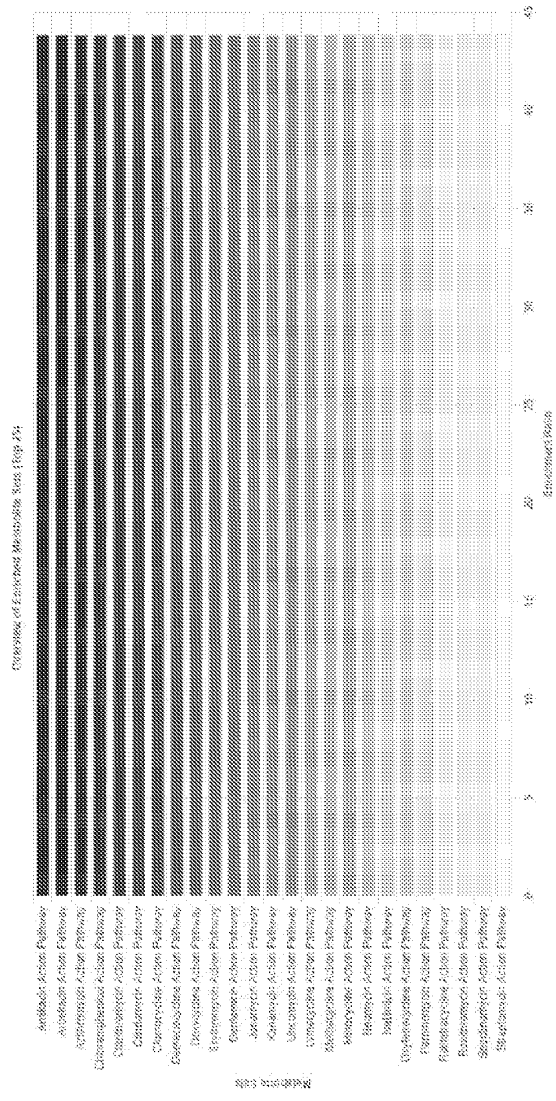
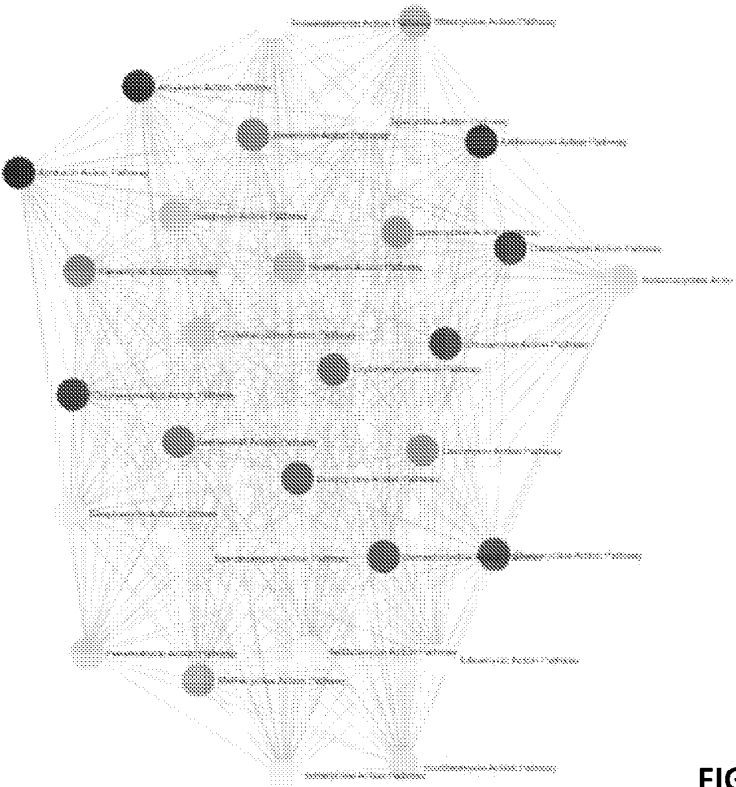


FIG. 50A





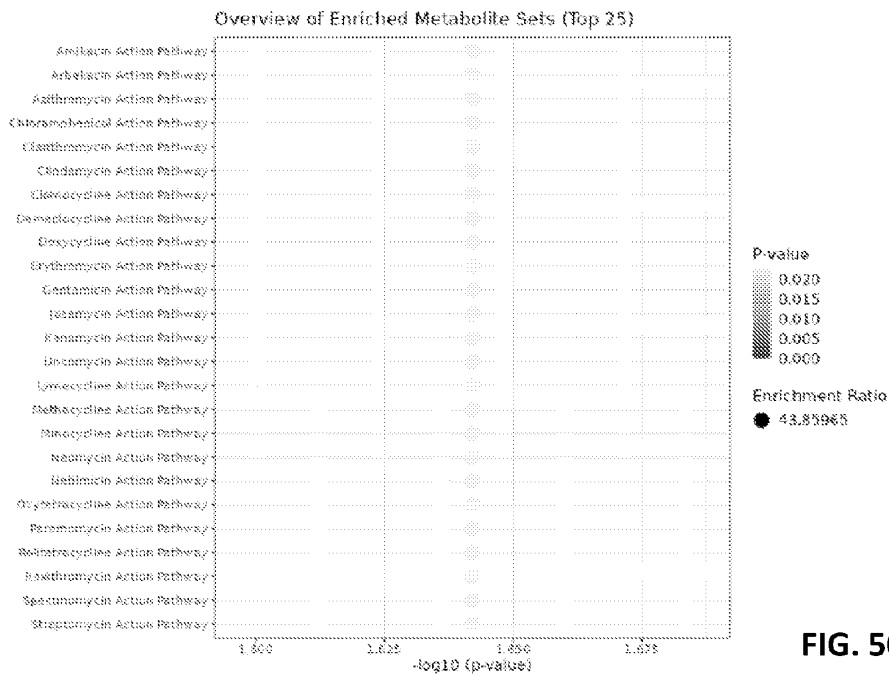


FIG. 50C

[illegible]

**FIG. 50D (continued)**

[illegible]

**FIG. 50D (continued)**

[illegible]

**FIG. 50D**

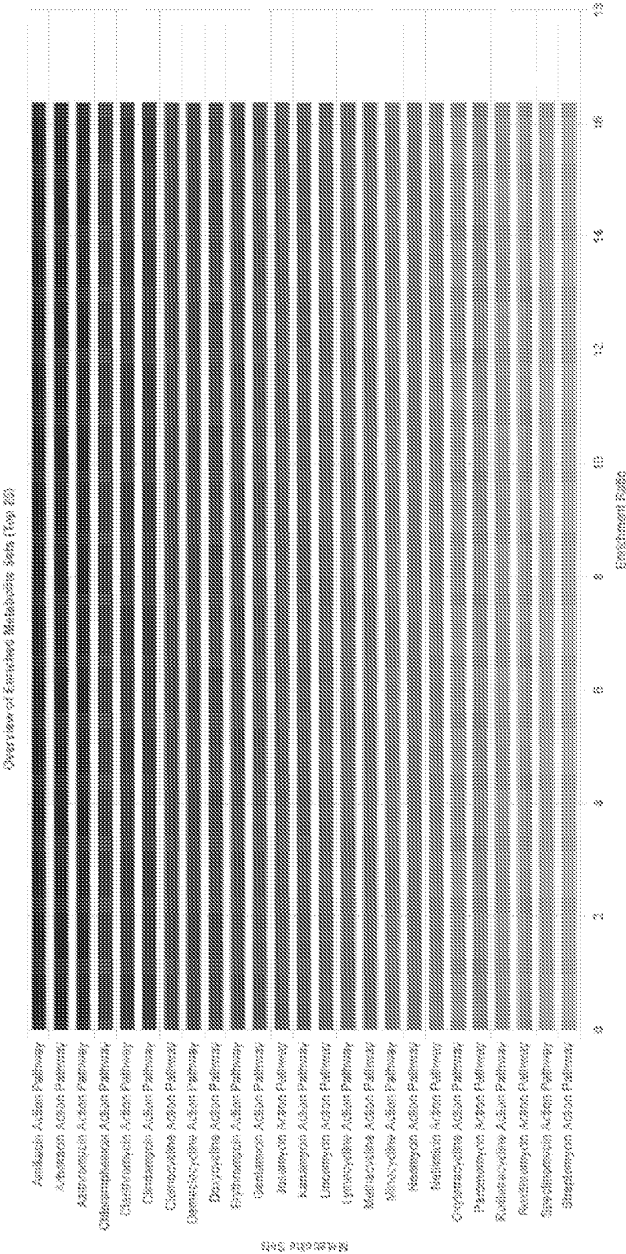


FIG. 50E

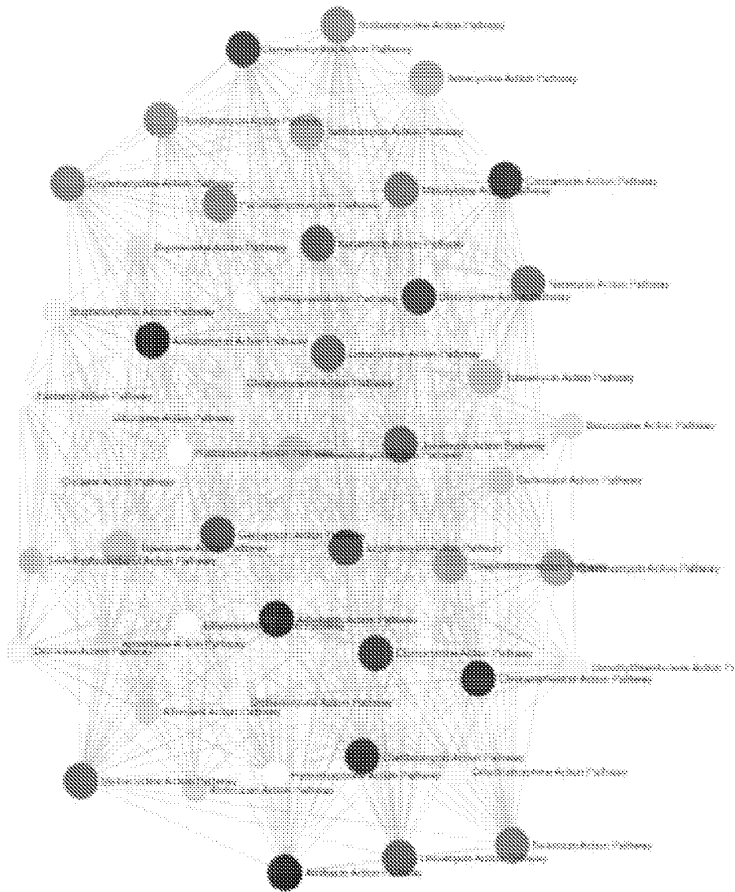


FIG. 50F

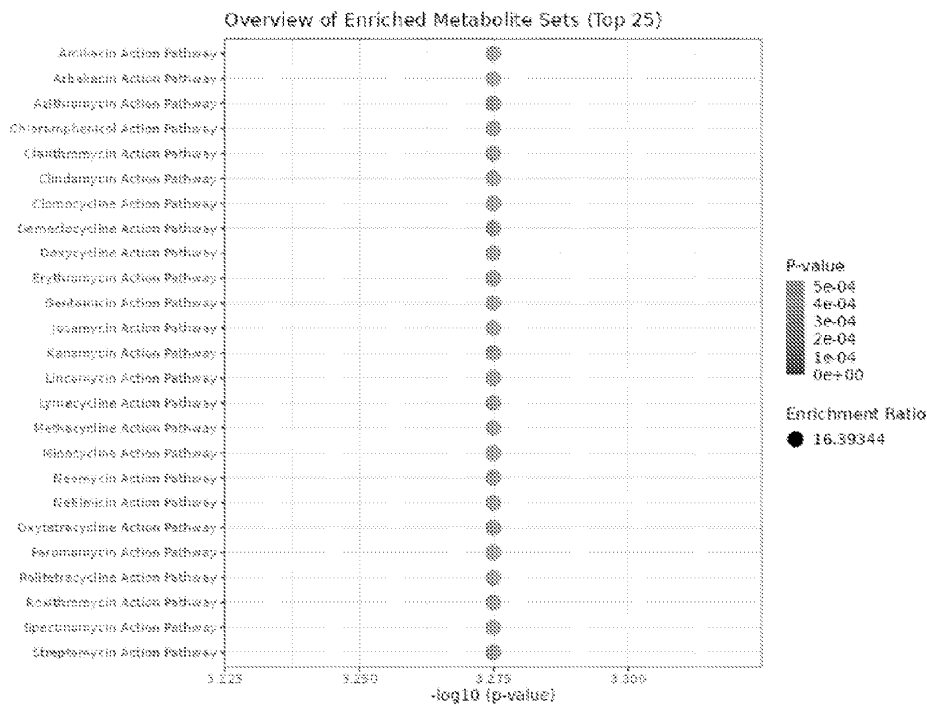


FIG. 50G



[illegible]

**FIG. 50H (continued)**

| Reaction/Route Step       | Reagent                | Temp | Time | Yield (%) | Purity (%) | Notes            |
|---------------------------|------------------------|------|------|-----------|------------|------------------|
| Reaction 1: A + B → C     | Reagent A, Reagent B   | 0 °C | 1 h  | 85        | 95         | Colorless solid  |
| Reaction 2: C + D → E     | Reagent C, Reagent D   | 0 °C | 1 h  | 80        | 90         | White solid      |
| Reaction 3: E + F → G     | Reagent E, Reagent F   | 0 °C | 1 h  | 75        | 85         | Yellow solid     |
| Reaction 4: G + H → I     | Reagent G, Reagent H   | 0 °C | 1 h  | 70        | 80         | Orange solid     |
| Reaction 5: I + J → K     | Reagent I, Reagent J   | 0 °C | 1 h  | 65        | 75         | Red solid        |
| Reaction 6: K + L → M     | Reagent K, Reagent L   | 0 °C | 1 h  | 60        | 70         | Brown solid      |
| Reaction 7: M + N → O     | Reagent M, Reagent N   | 0 °C | 1 h  | 55        | 65         | Dark brown solid |
| Reaction 8: O + P → Q     | Reagent O, Reagent P   | 0 °C | 1 h  | 50        | 60         | Black solid      |
| Reaction 9: Q + R → S     | Reagent Q, Reagent R   | 0 °C | 1 h  | 45        | 55         | Dark grey solid  |
| Reaction 10: S + T → U    | Reagent S, Reagent T   | 0 °C | 1 h  | 40        | 50         | Black solid      |
| Reaction 11: U + V → W    | Reagent U, Reagent V   | 0 °C | 1 h  | 35        | 45         | Black solid      |
| Reaction 12: W + X → Y    | Reagent W, Reagent X   | 0 °C | 1 h  | 30        | 40         | Black solid      |
| Reaction 13: Y + Z → AA   | Reagent Y, Reagent Z   | 0 °C | 1 h  | 25        | 35         | Black solid      |
| Reaction 14: AA + BB → CC | Reagent AA, Reagent BB | 0 °C | 1 h  | 20        | 30         | Black solid      |
| Reaction 15: CC + DD → EE | Reagent CC, Reagent DD | 0 °C | 1 h  | 15        | 25         | Black solid      |
| Reaction 16: EE + FF → GG | Reagent EE, Reagent FF | 0 °C | 1 h  | 10        | 20         | Black solid      |
| Reaction 17: GG + HH → II | Reagent GG, Reagent HH | 0 °C | 1 h  | 5         | 15         | Black solid      |
| Reaction 18: II + JJ → KK | Reagent II, Reagent JJ | 0 °C | 1 h  | 0         | 10         | Black solid      |
| Reaction 19: KK + LL → MM | Reagent KK, Reagent LL | 0 °C | 1 h  | 0         | 5          | Black solid      |
| Reaction 20: MM + NN → OO | Reagent MM, Reagent NN | 0 °C | 1 h  | 0         | 0          | Black solid      |

FIG. 50H (continued)

| Mechanism Set                  | Model | Units | Expected | P-value | Median P | FSHR  | Details |
|--------------------------------|-------|-------|----------|---------|----------|-------|---------|
| Cytosolic Action Pathway       | 10    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 11    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Cytosolic Action Pathway       | 18    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 19    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Peroxisomal Action Pathway     | 13    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 15    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Mitochondrial Action Pathway   | 12    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 14    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Endoplasmic Action Pathway     | 16    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 17    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Golgi Action Pathway           | 19    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 15    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Lysosomal Action Pathway       | 13    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 14    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Vacuolar Action Pathway        | 16    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 17    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Plasma Membrane Action Pathway | 10    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 11    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Cytoskeleton Action Pathway    | 18    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 19    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Mitochondrial Action Pathway   | 13    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 15    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Lysosomal Action Pathway       | 12    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 14    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Vacuolar Action Pathway        | 16    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 17    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Plasma Membrane Action Pathway | 10    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 11    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Cytoskeleton Action Pathway    | 18    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 19    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Mitochondrial Action Pathway   | 13    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 15    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Lysosomal Action Pathway       | 12    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 14    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Vacuolar Action Pathway        | 16    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 17    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Plasma Membrane Action Pathway | 10    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 11    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Cytoskeleton Action Pathway    | 18    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 19    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Mitochondrial Action Pathway   | 13    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 15    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Lysosomal Action Pathway       | 12    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 14    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Vacuolar Action Pathway        | 16    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 17    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Plasma Membrane Action Pathway | 10    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 11    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Cytoskeleton Action Pathway    | 18    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 19    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Mitochondrial Action Pathway   | 13    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 15    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Lysosomal Action Pathway       | 12    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 14    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Vacuolar Action Pathway        | 16    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 17    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Plasma Membrane Action Pathway | 10    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 11    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Cytoskeleton Action Pathway    | 18    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 19    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Mitochondrial Action Pathway   | 13    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 15    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Lysosomal Action Pathway       | 12    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 14    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Vacuolar Action Pathway        | 16    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 17    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Plasma Membrane Action Pathway | 10    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 11    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Cytoskeleton Action Pathway    | 18    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 19    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Mitochondrial Action Pathway   | 13    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 15    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Lysosomal Action Pathway       | 12    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 14    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Vacuolar Action Pathway        | 16    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 17    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Plasma Membrane Action Pathway | 10    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 11    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Cytoskeleton Action Pathway    | 18    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 19    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Mitochondrial Action Pathway   | 13    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 15    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Lysosomal Action Pathway       | 12    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 14    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Vacuolar Action Pathway        | 16    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 17    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Plasma Membrane Action Pathway | 10    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 11    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Cytoskeleton Action Pathway    | 18    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 19    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Mitochondrial Action Pathway   | 13    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 15    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Lysosomal Action Pathway       | 12    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 14    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Vacuolar Action Pathway        | 16    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 17    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Plasma Membrane Action Pathway | 10    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 11    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Cytoskeleton Action Pathway    | 18    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 19    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Mitochondrial Action Pathway   | 13    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 15    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Lysosomal Action Pathway       | 12    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 14    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Vacuolar Action Pathway        | 16    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 17    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Plasma Membrane Action Pathway | 10    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 11    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Cytoskeleton Action Pathway    | 18    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 19    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Mitochondrial Action Pathway   | 13    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 15    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Lysosomal Action Pathway       | 12    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 14    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Vacuolar Action Pathway        | 16    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 17    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Plasma Membrane Action Pathway | 10    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 11    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Cytoskeleton Action Pathway    | 18    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 19    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Mitochondrial Action Pathway   | 13    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 15    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Lysosomal Action Pathway       | 12    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 14    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Vacuolar Action Pathway        | 16    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 17    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Plasma Membrane Action Pathway | 10    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 11    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Cytoskeleton Action Pathway    | 18    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 19    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Mitochondrial Action Pathway   | 13    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 15    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Lysosomal Action Pathway       | 12    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 14    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Vacuolar Action Pathway        | 16    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 17    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Plasma Membrane Action Pathway | 10    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 11    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Cytoskeleton Action Pathway    | 18    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 19    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Mitochondrial Action Pathway   | 13    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 15    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Lysosomal Action Pathway       | 12    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 14    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Vacuolar Action Pathway        | 16    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 17    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Plasma Membrane Action Pathway | 10    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 11    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Cytoskeleton Action Pathway    | 18    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 19    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Mitochondrial Action Pathway   | 13    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 15    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Lysosomal Action Pathway       | 12    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 14    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Vacuolar Action Pathway        | 16    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 17    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Plasma Membrane Action Pathway | 10    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 11    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Cytoskeleton Action Pathway    | 18    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 19    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Mitochondrial Action Pathway   | 13    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 15    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Lysosomal Action Pathway       | 12    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 14    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Vacuolar Action Pathway        | 16    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 17    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Plasma Membrane Action Pathway | 10    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 11    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Cytoskeleton Action Pathway    | 18    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 19    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Mitochondrial Action Pathway   | 13    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 15    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Lysosomal Action Pathway       | 12    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 14    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Vacuolar Action Pathway        | 16    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 17    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Plasma Membrane Action Pathway | 10    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 11    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Cytoskeleton Action Pathway    | 18    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 19    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Mitochondrial Action Pathway   | 13    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 15    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
| Lysosomal Action Pathway       | 12    | 1     | 0.1      | 0.0005  | 0.0      | 0.473 | View    |
|                                | 14    | 1     | 0.1      |         |          |       |         |

**FIG. 50H (continued)**

[illegible]

**FIG. 50H (continued)**



| Metabolite Set                              | Total | Path | Expected | P-value | Holm-P | FDR   | Details |
|---------------------------------------------|-------|------|----------|---------|--------|-------|---------|
| Thioquantine Action Pathway                 | 87    | 1    | 0.795    | 0.184   | 1.0    | 0.878 | View    |
| Imipramine Action Pathway                   | 52    | 1    | 0.251    | 0.189   | 1.0    | 0.276 | View    |
| Acetylcholine Action Pathway                | 88    | 2    | 0.304    | 0.188   | 1.0    | 0.681 | View    |
| Lidocaine (Local Anesthetic) Action Pathway | 26    | 1    | 0.257    | 0.211   | 1.0    | 0.773 | View    |
| Chloroquine Action Pathway                  | 27    | 1    | 0.247    | 0.222   | 1.0    | 0.799 | View    |
| Methamphetamine Action Pathway              | 20    | 1    | 0.171    | 0.244   | 1.0    | 0.954 | View    |
| Risperidone Action Pathway                  | 34    | 1    | 0.311    | 0.272   | 1.0    | 0.999 | View    |

FIG. 50H

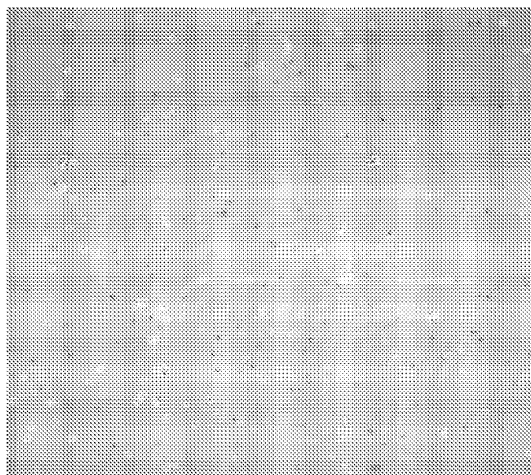


Image from Cell Counter Countess III – live cells are bright.

FIG. 51A

Retrieved after 188h  
of cryopreservation

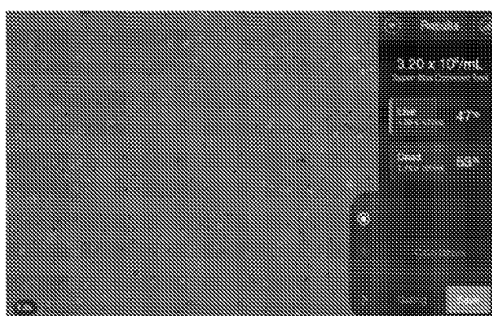


Image from Cell Counter Countess III – live cells are bright.

FIG. 51B