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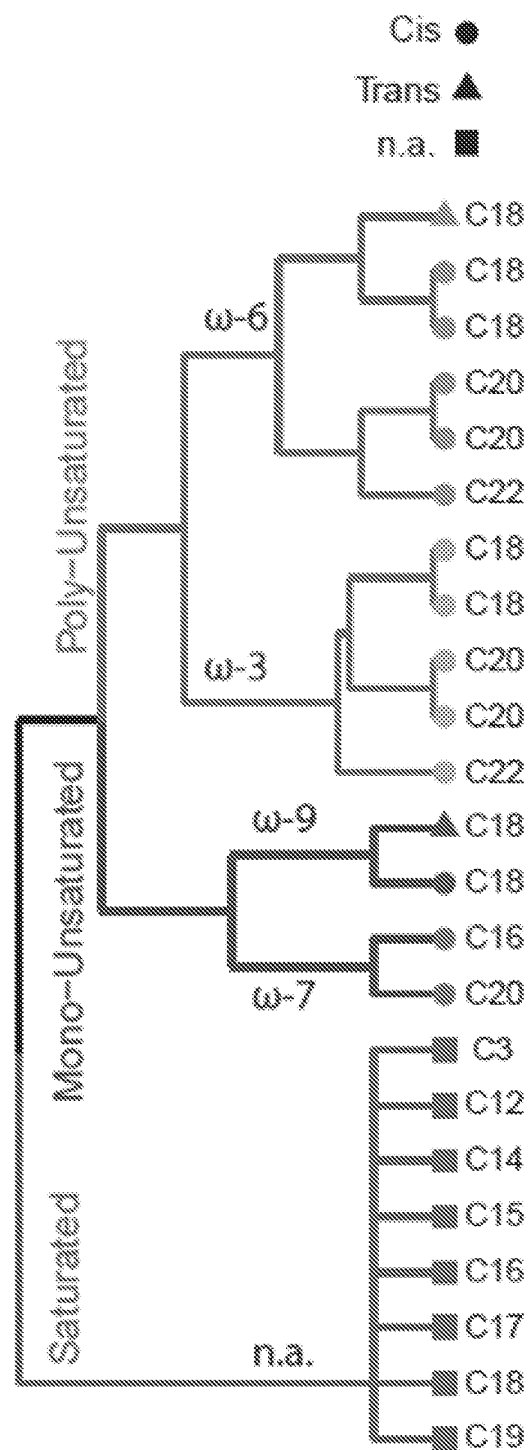


FIG. 1A



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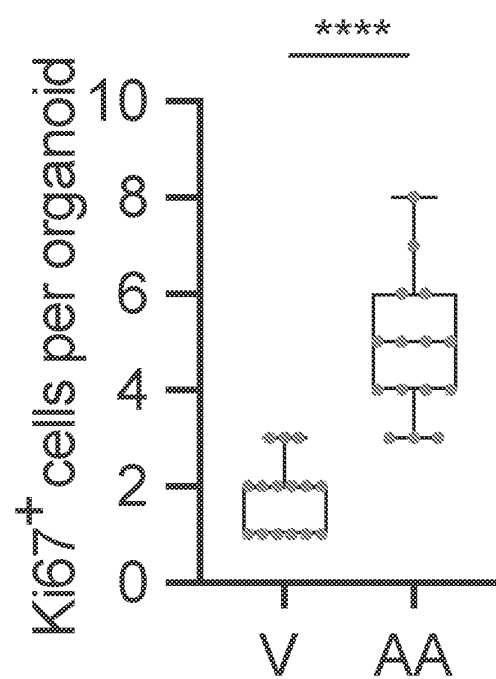


FIG. 1E

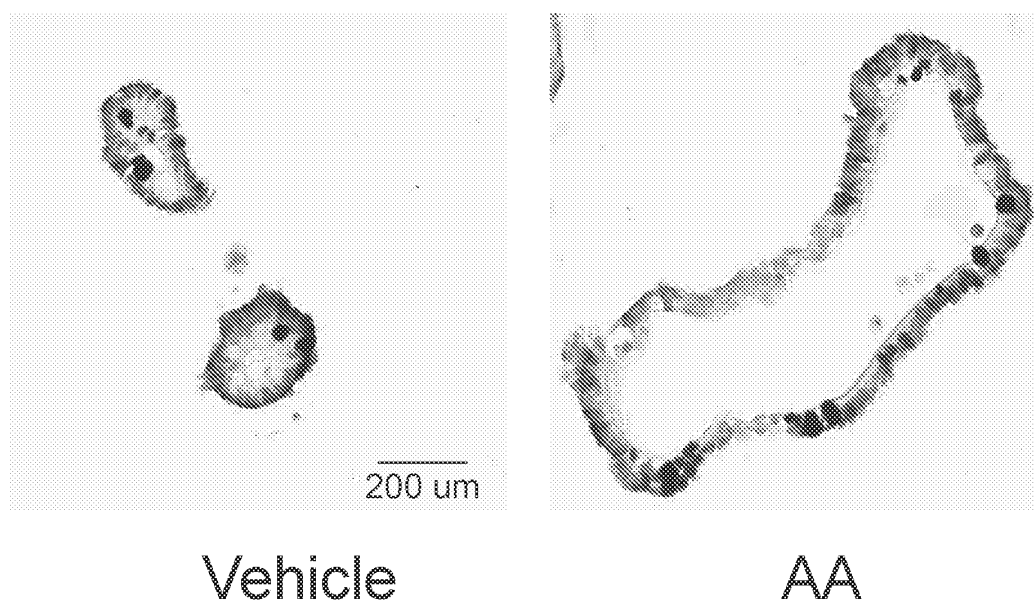


FIG. 1F

SUBSTITUTE SHEET (RULE 26)

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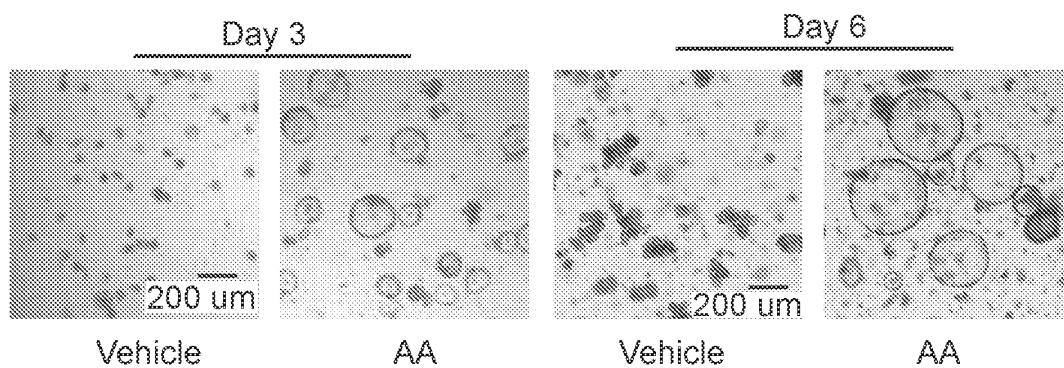


FIG. 1G

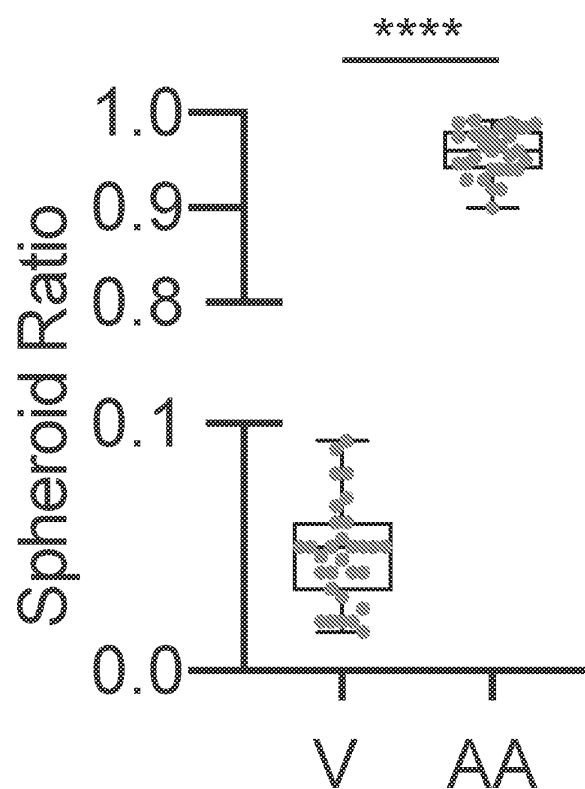


FIG. 1H

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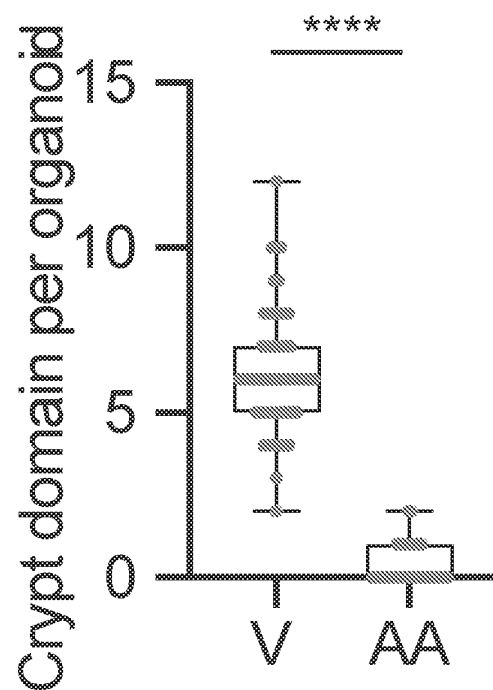


FIG. 1I

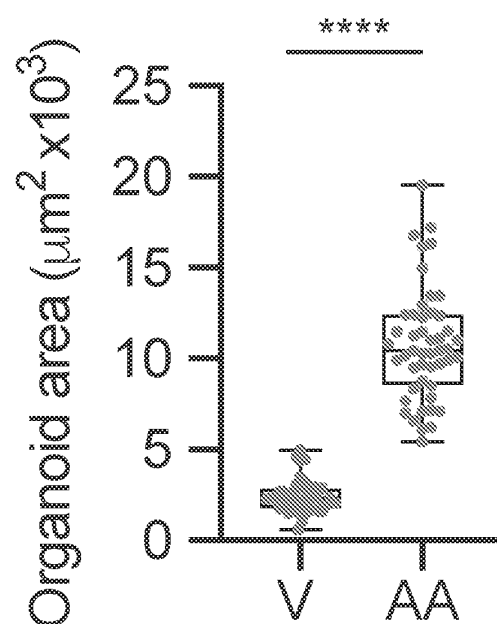
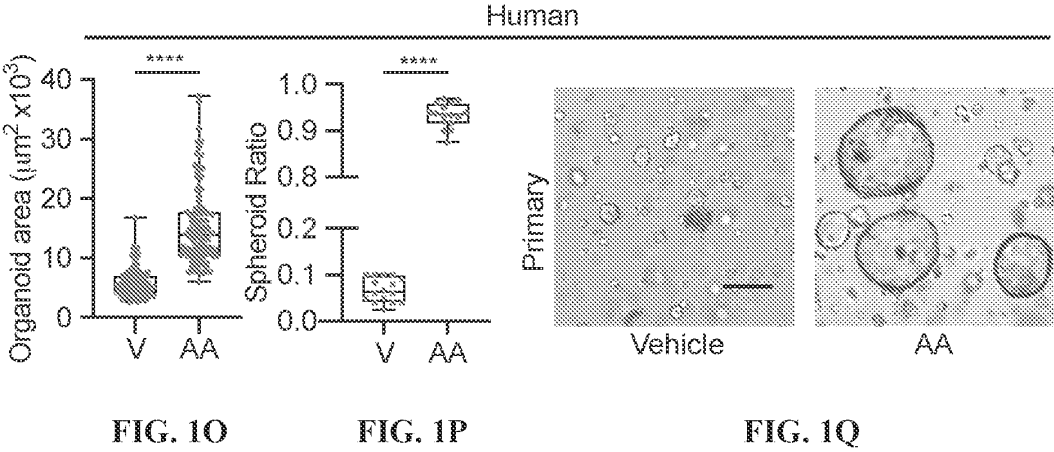
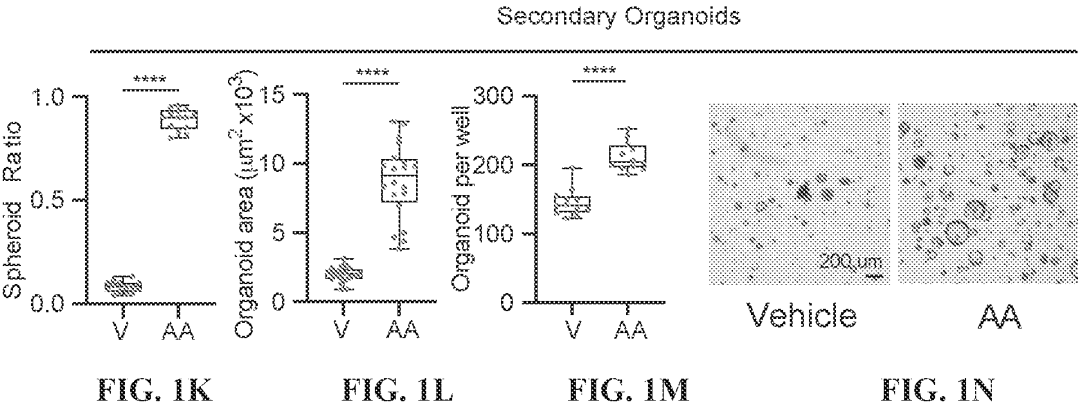


FIG. 1J

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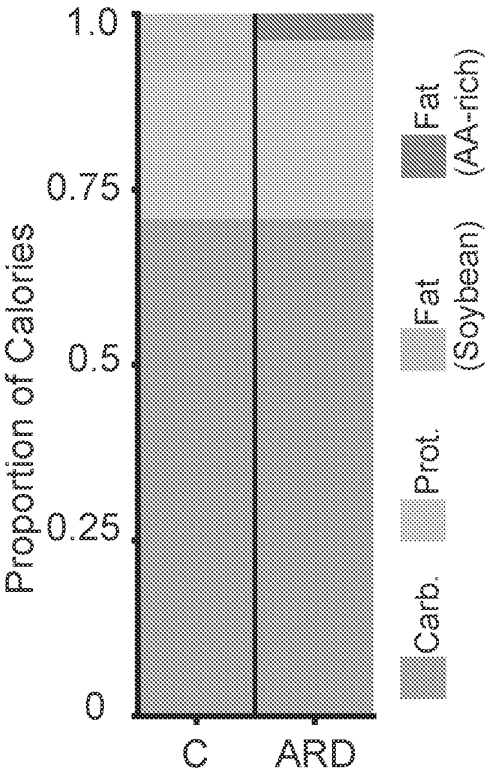
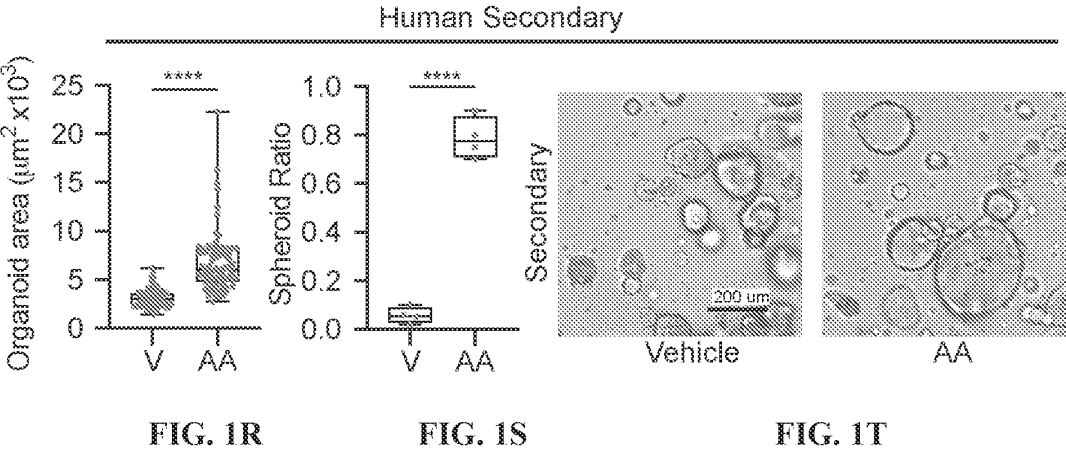


FIG. 2A

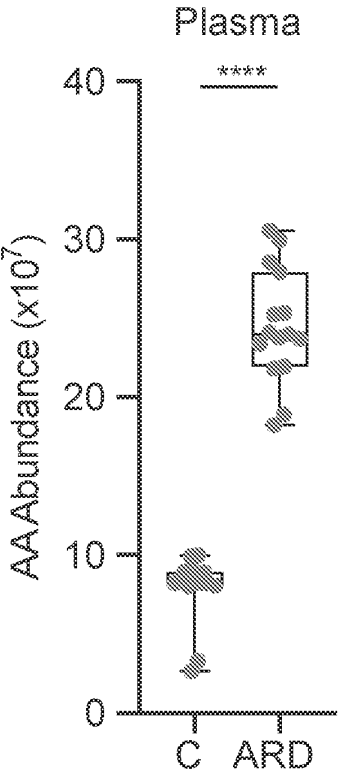


FIG. 2B

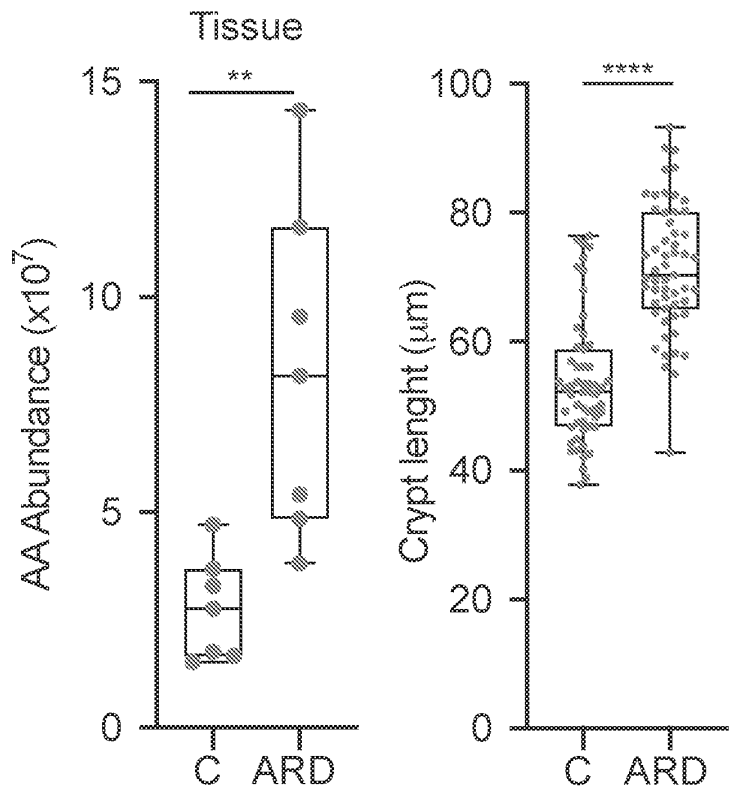


FIG. 2C

FIG. 2D

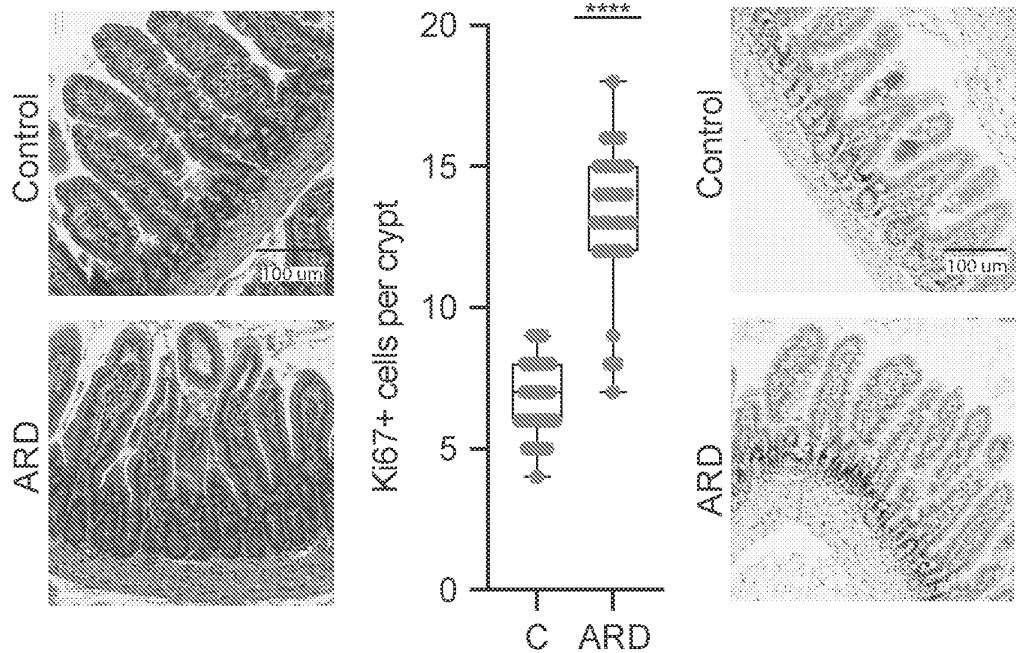


FIG. 2E

FIG. 2F

FIG. 2G

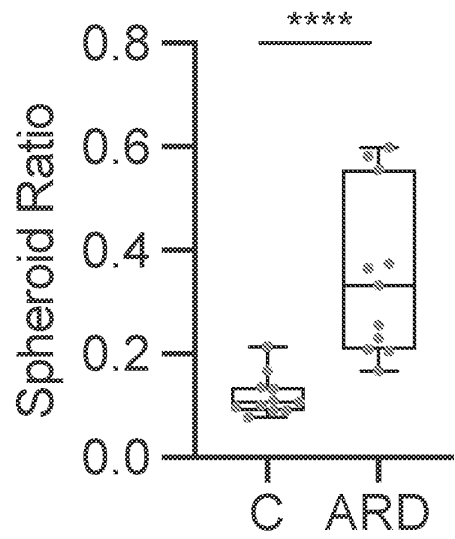


FIG. 2H

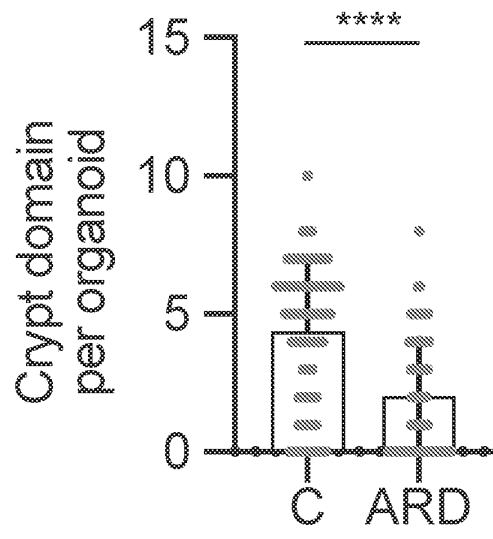


FIG. 2I

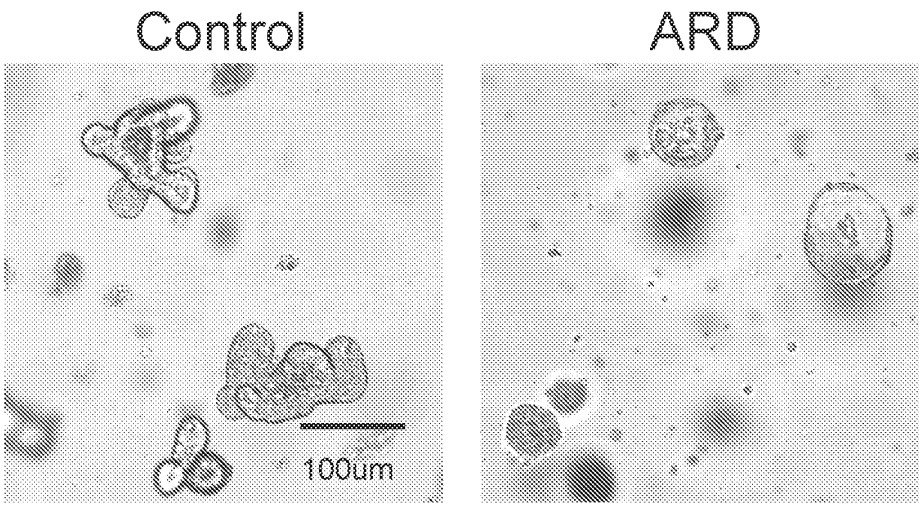


FIG. 2J

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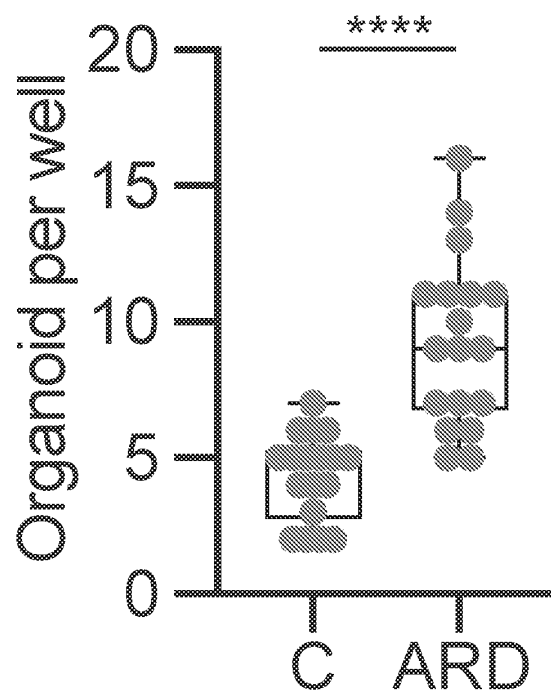


FIG. 2K

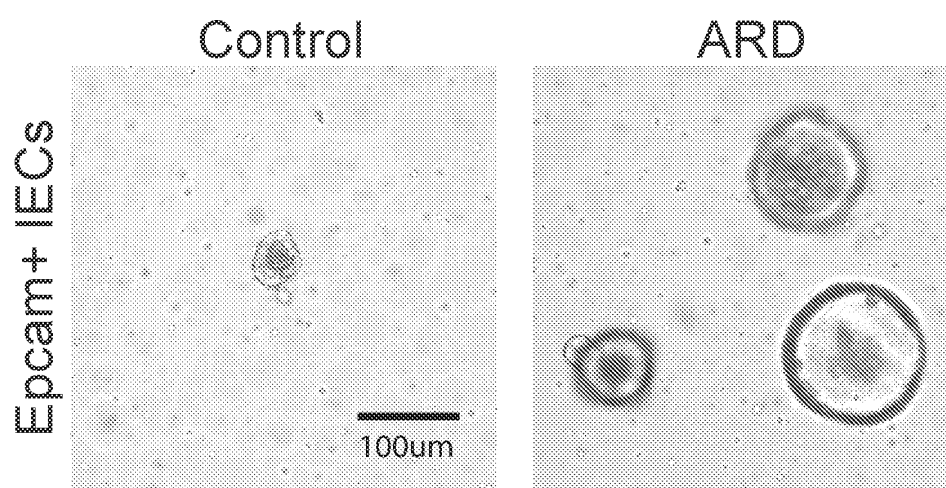


FIG. 2L

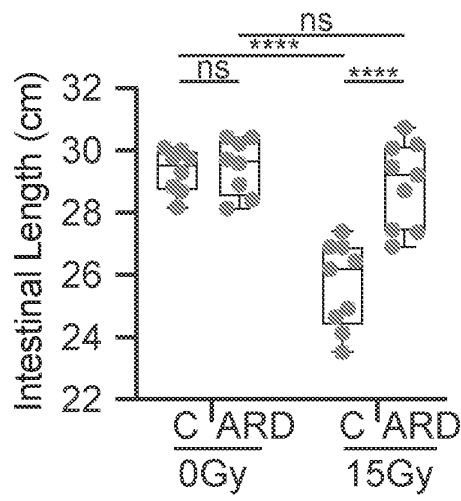


FIG. 2M

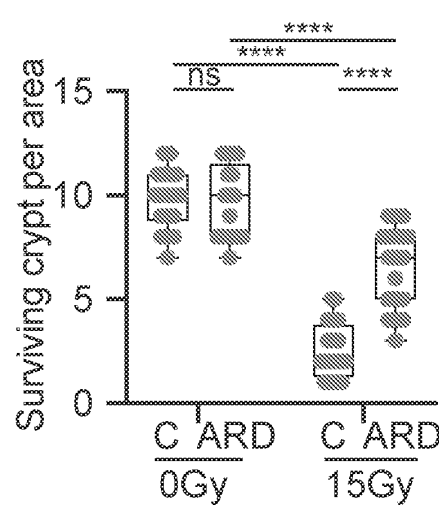


FIG. 2N

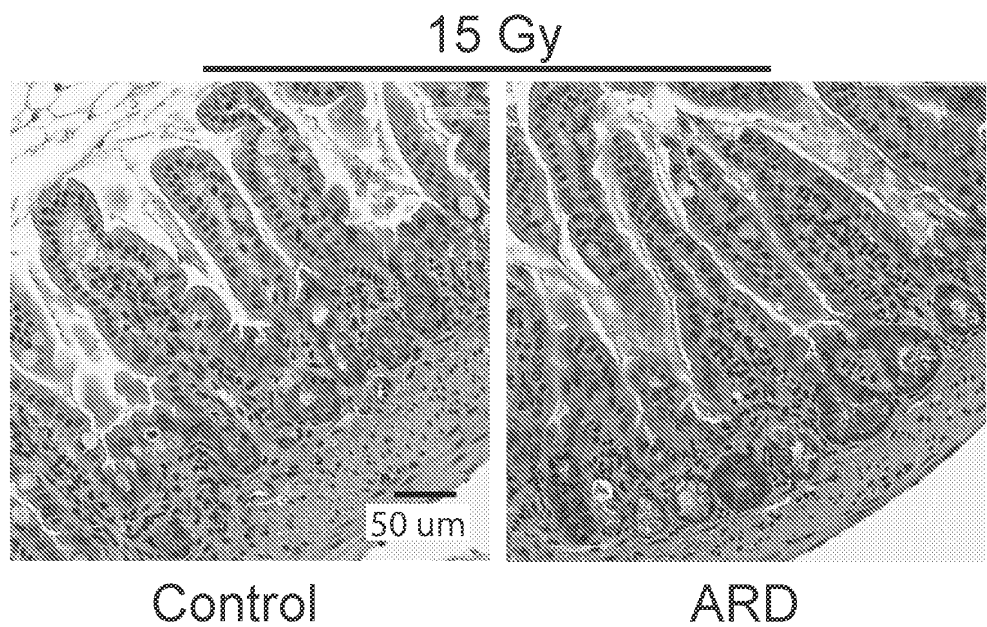


FIG. 2O

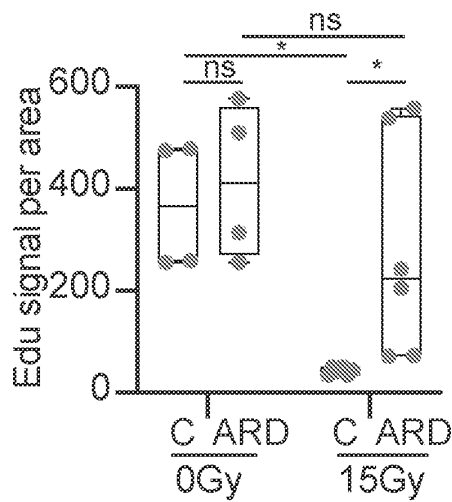


FIG. 2P

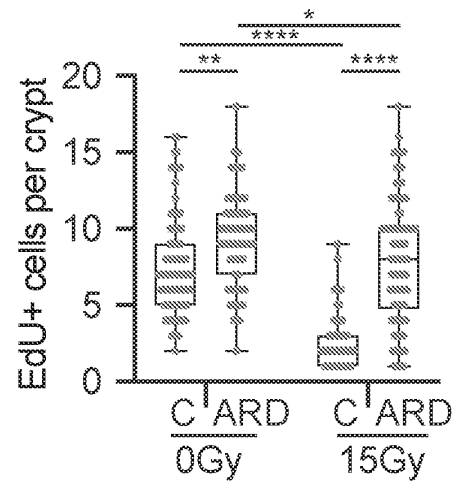


FIG. 2Q

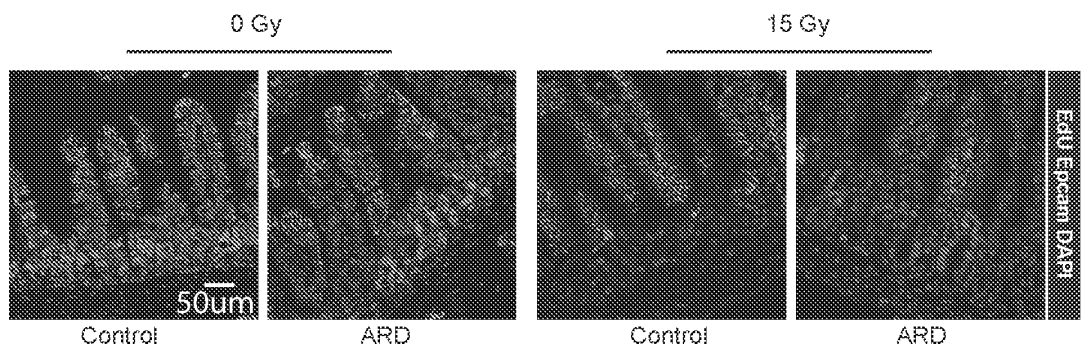


FIG. 2R

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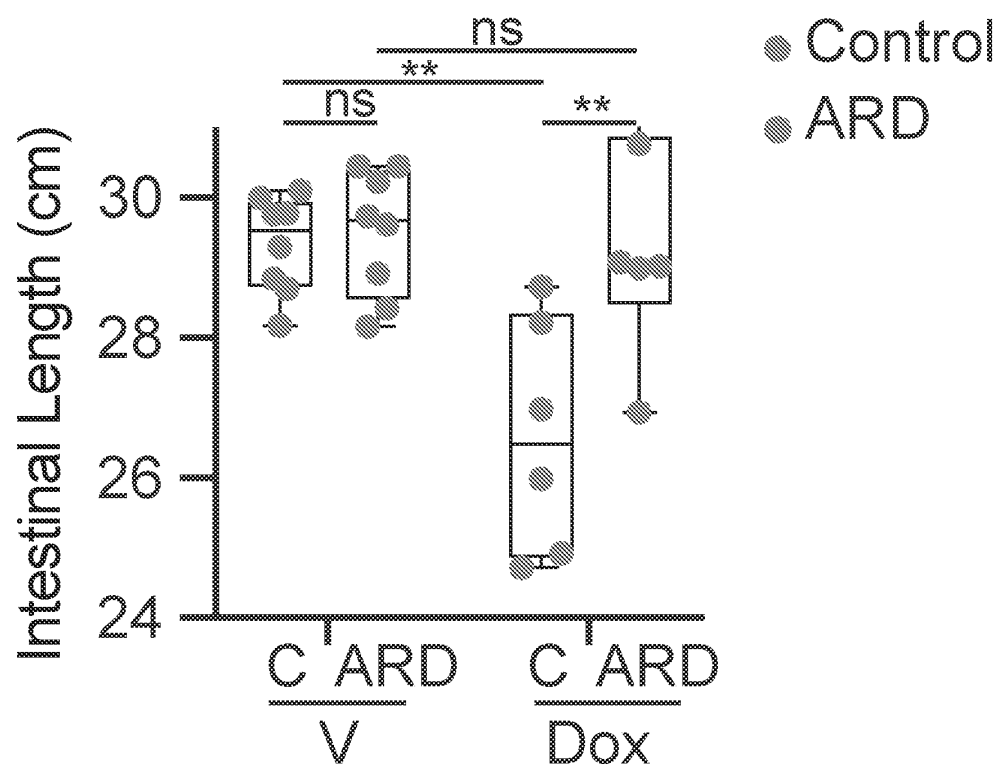


FIG. 2S

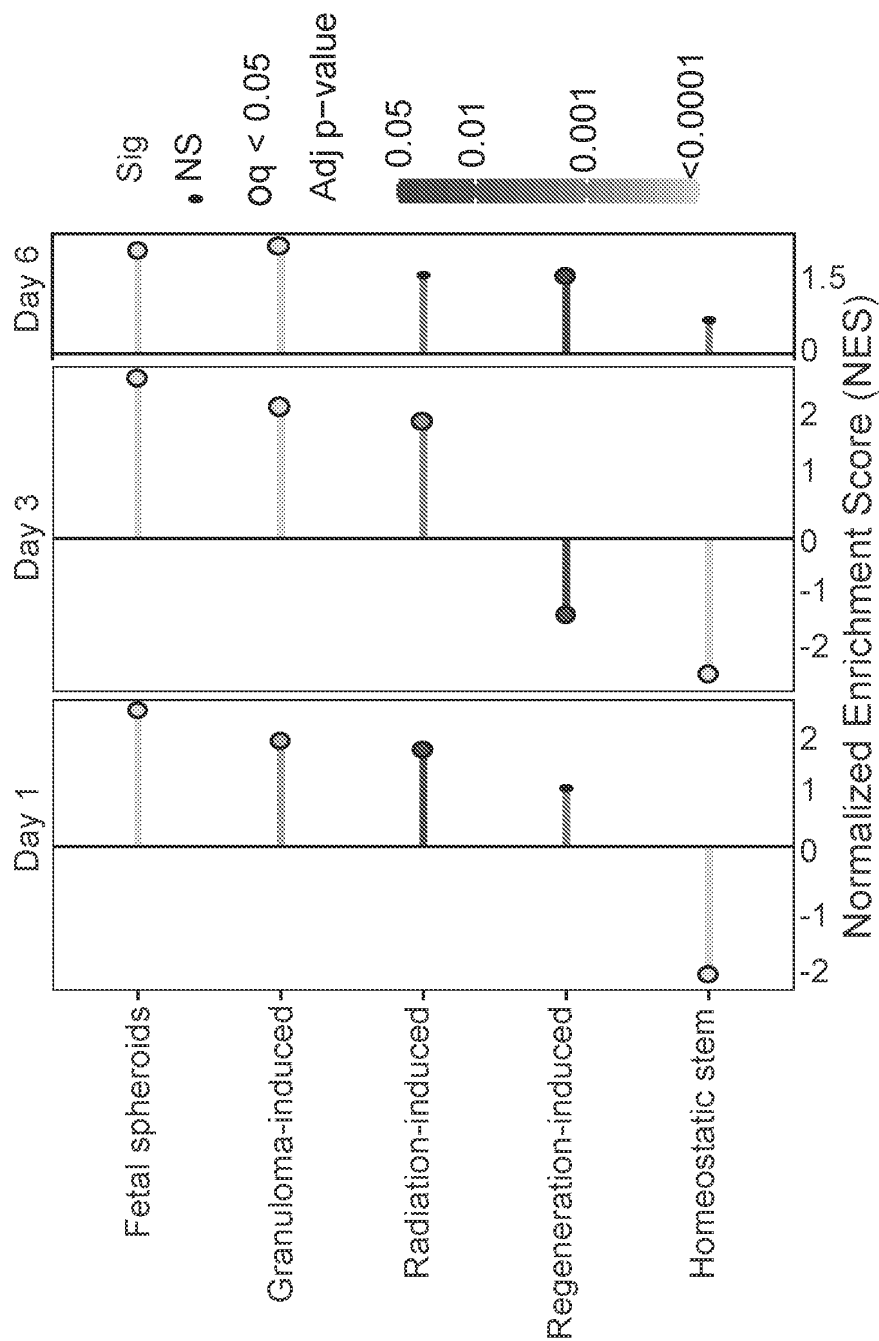


FIG. 3A

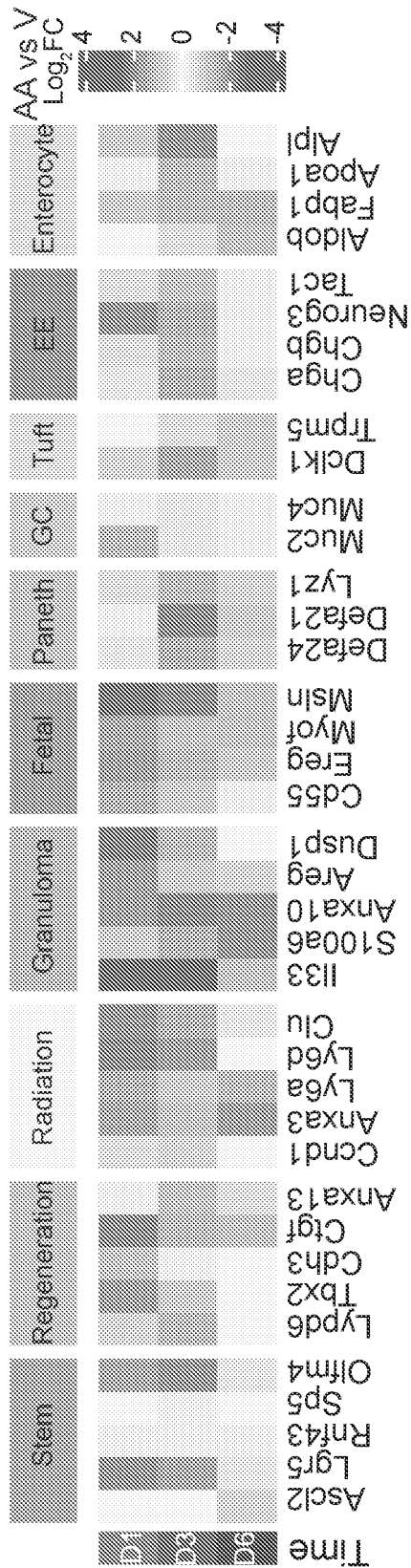


FIG. 3B

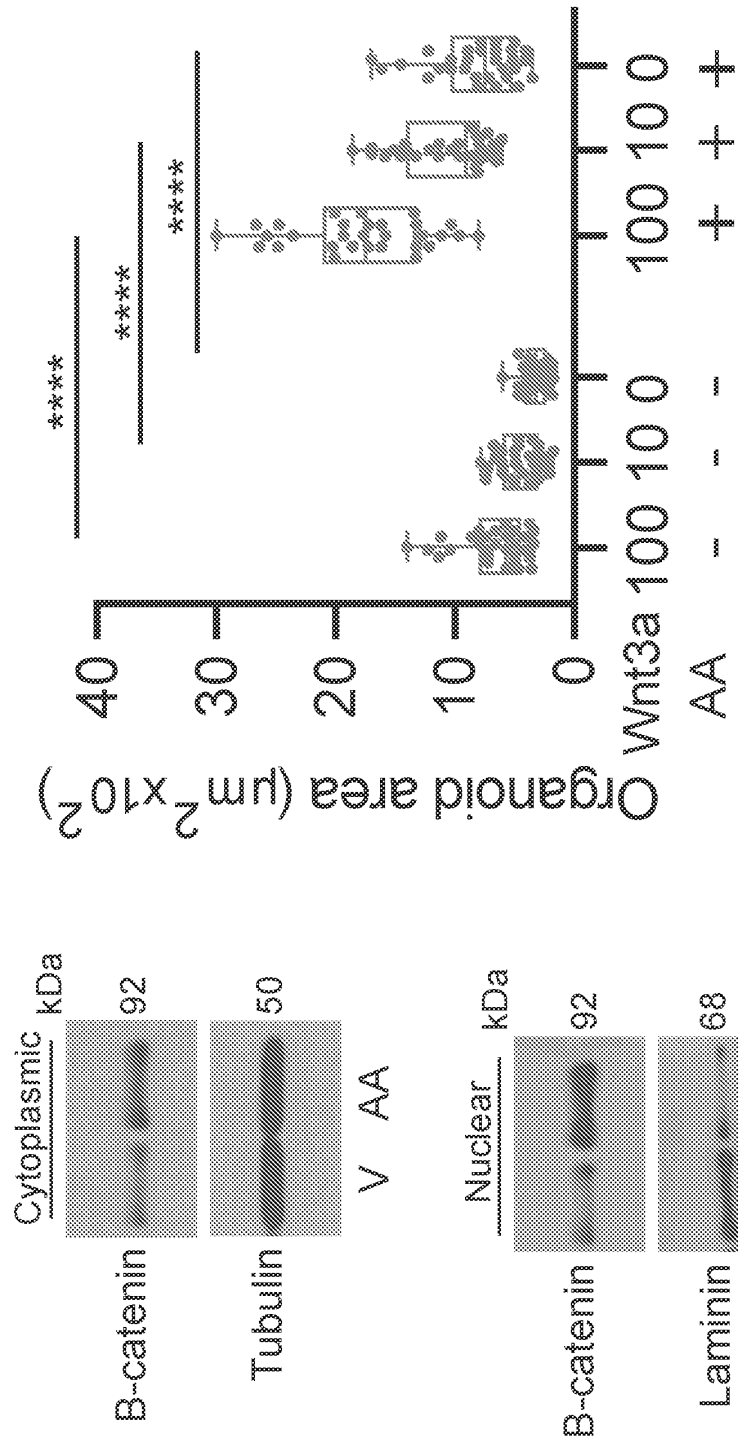


FIG. 3D

FIG. 3C

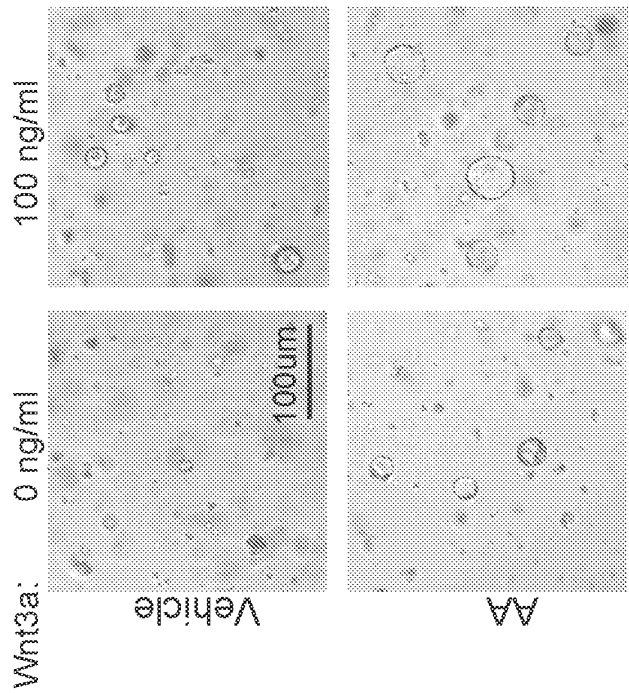


FIG. 3F

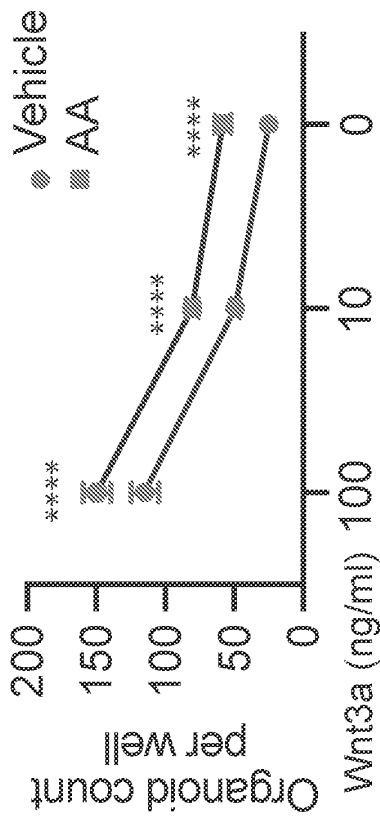


FIG. 3E

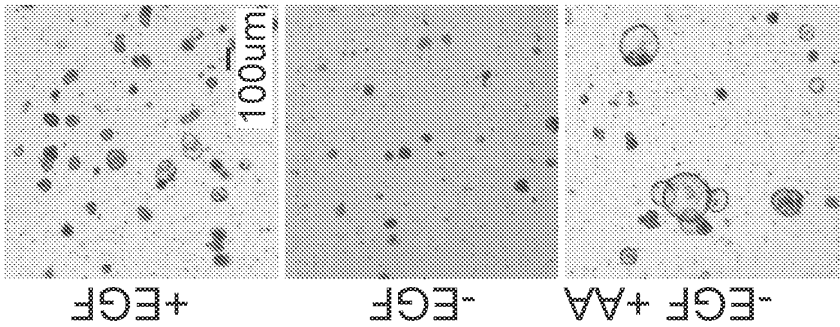


FIG. 3I

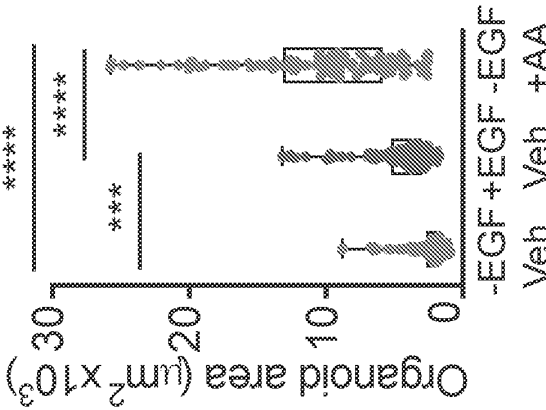


FIG. 3H

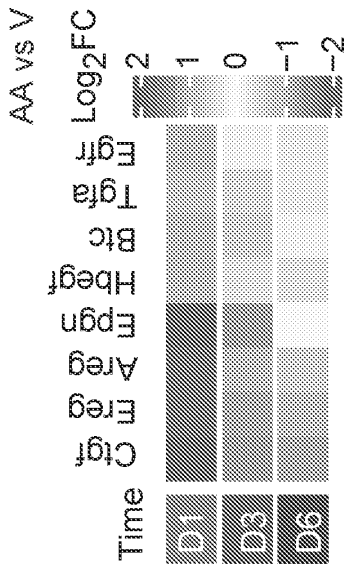


FIG. 3G

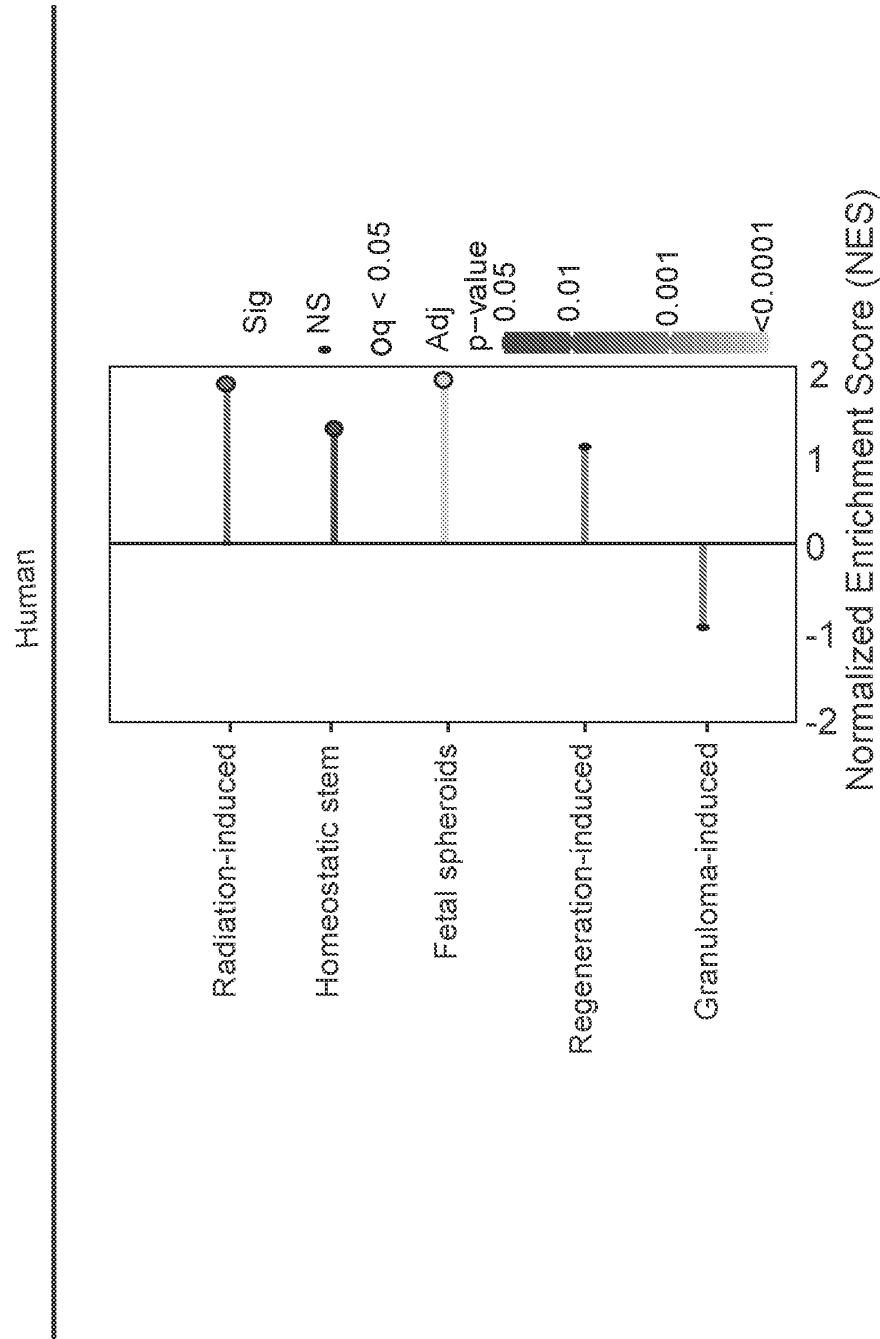


FIG. 3J

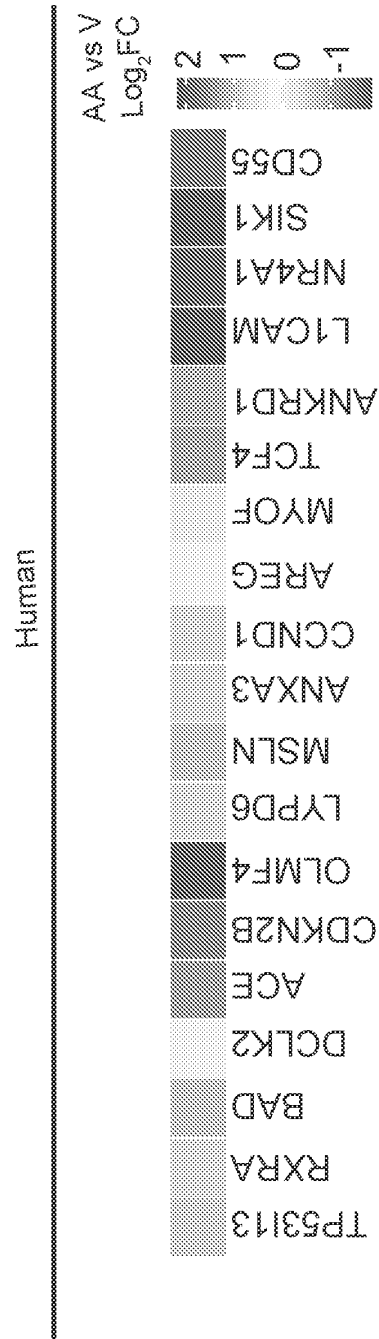


FIG. 3K

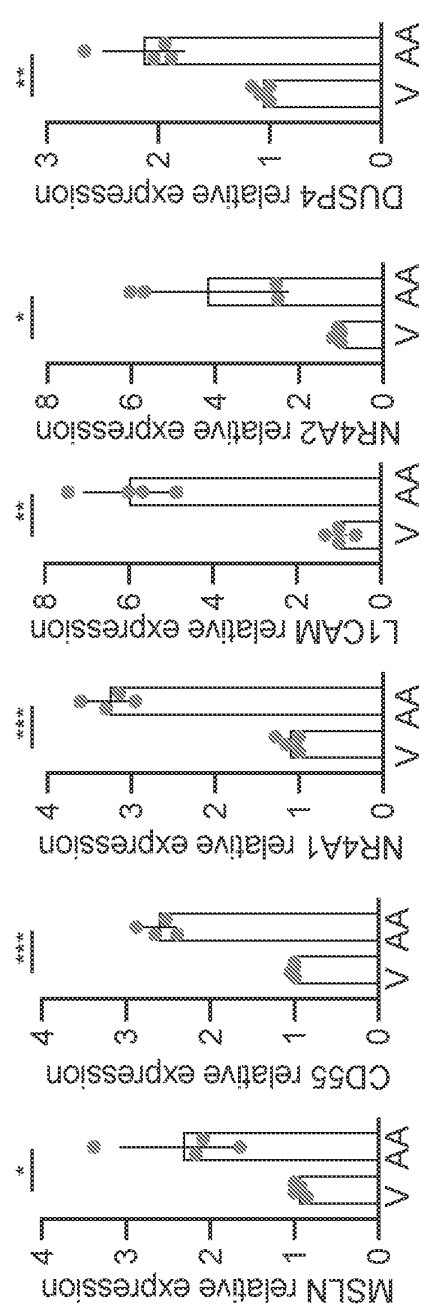


FIG. 3L

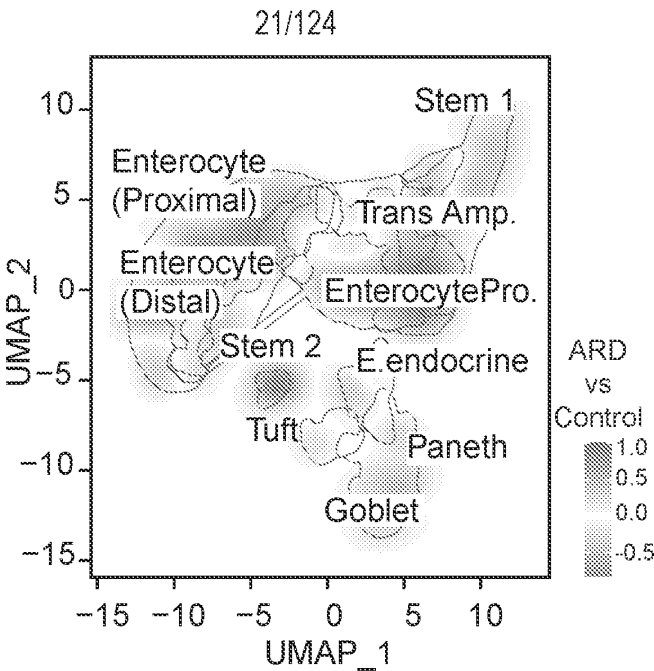
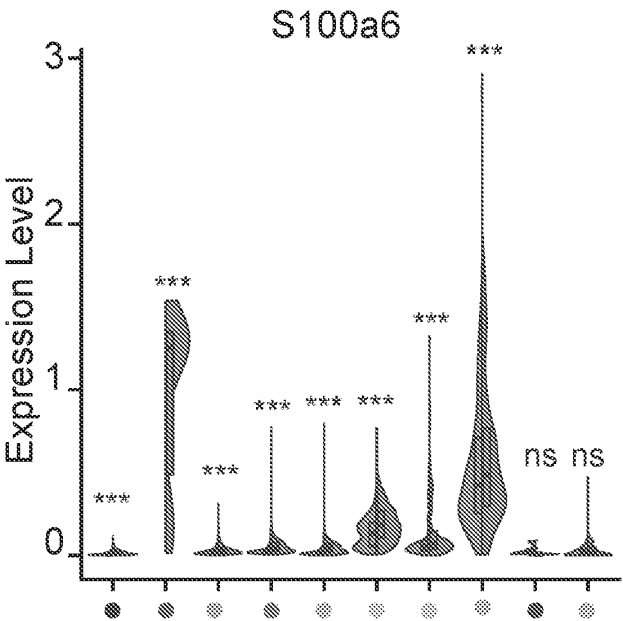


FIG. 4A

● Stem 1 ● Stem 2 ● Transit Amplifying ● Enterocyte Progenitor ● Enterocyte (Proximal)
● Enterocyte (Distal) ● Enteroendocrine ● Goblet ● Paneth ● Tuft
● Control
● ARD



● Stem 1 ● Stem 2 ● Transit Amplifying ● Enterocyte Progenitor ● Enterocyte (Proximal)
● Enterocyte (Distal) ● Enteroendocrine ● Goblet ● Paneth ● Tuft ● Control ● ARD

FIG. 4B

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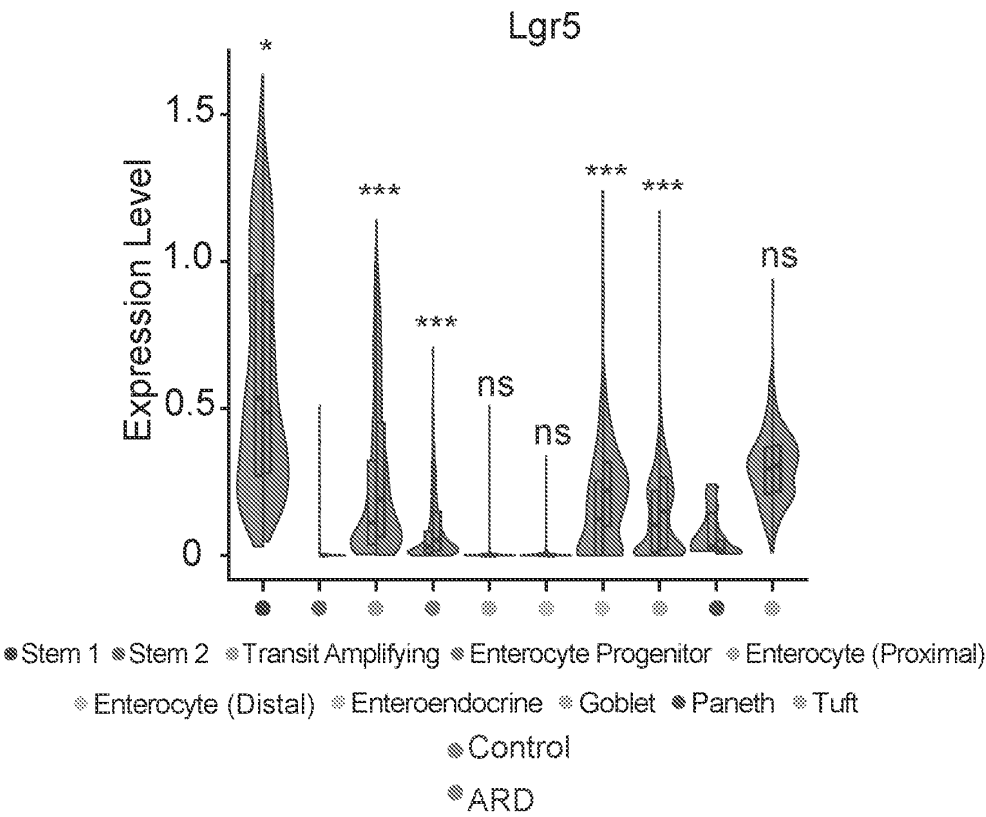


FIG. 4C

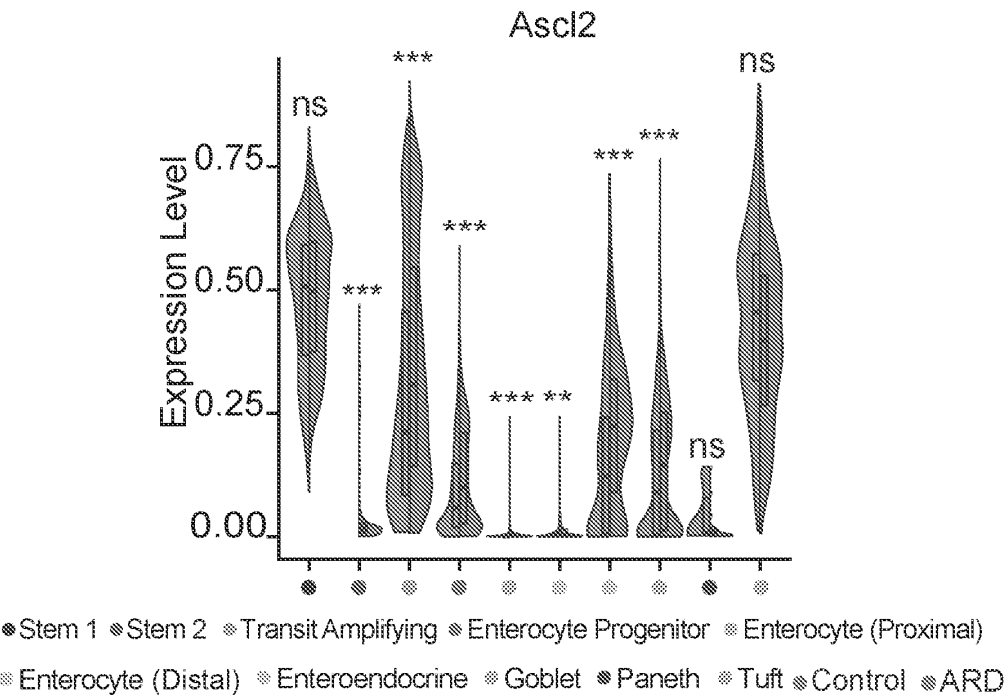


FIG. 4D

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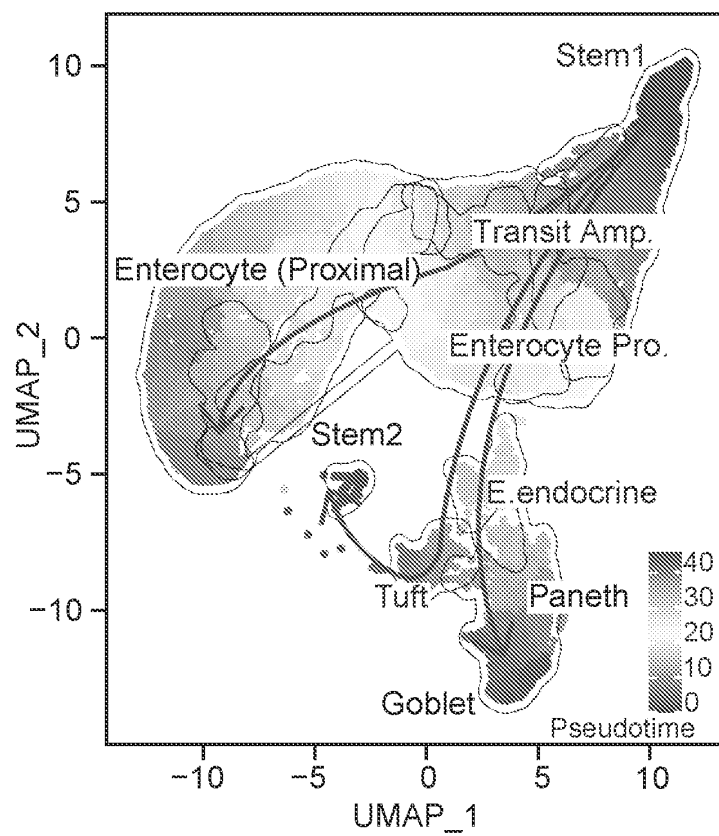


FIG. 4E

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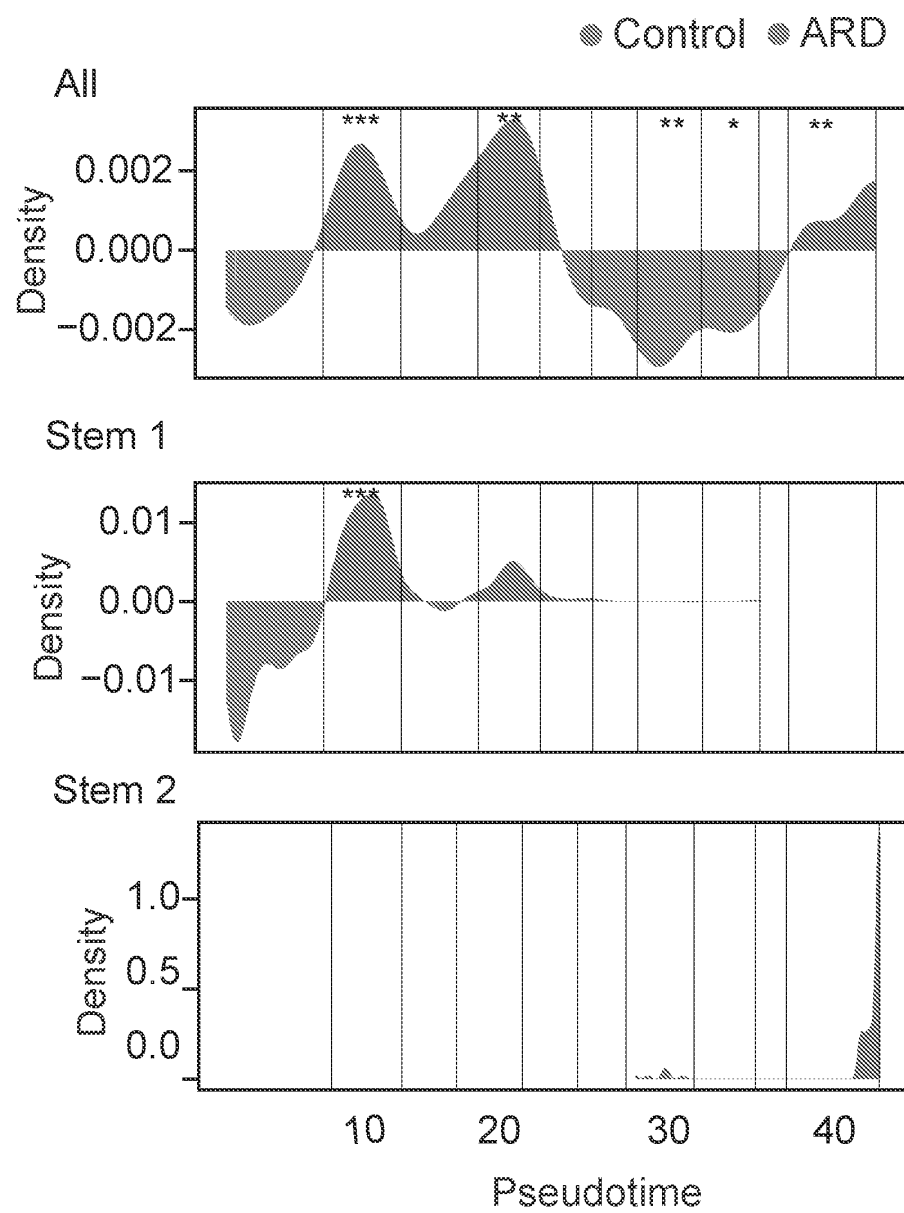


FIG. 4F

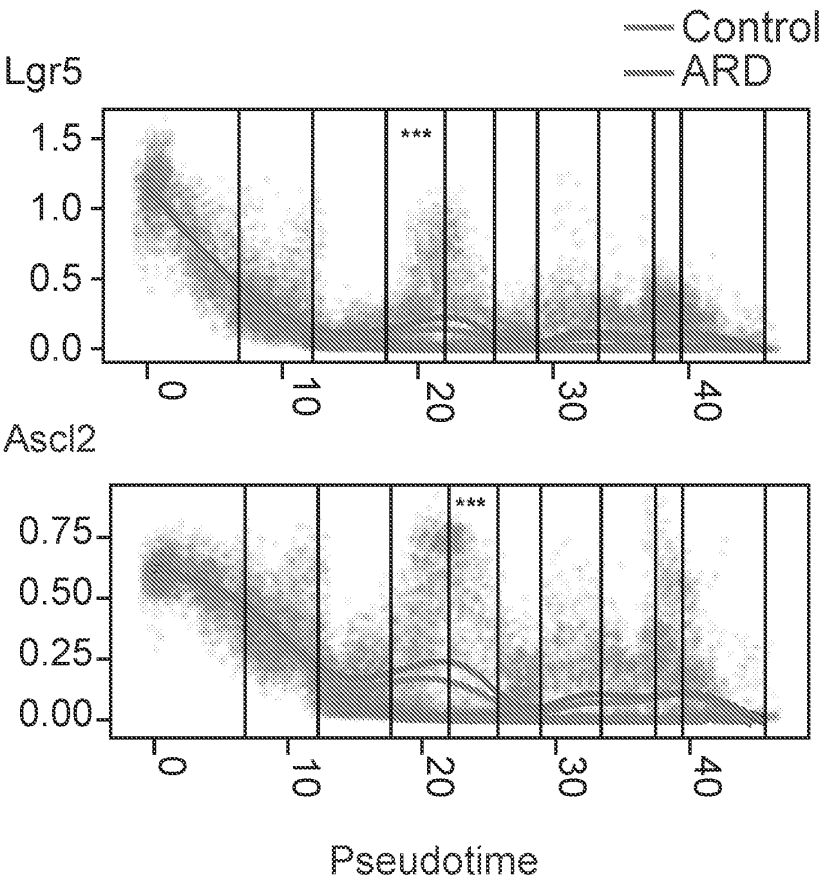


FIG. 4G

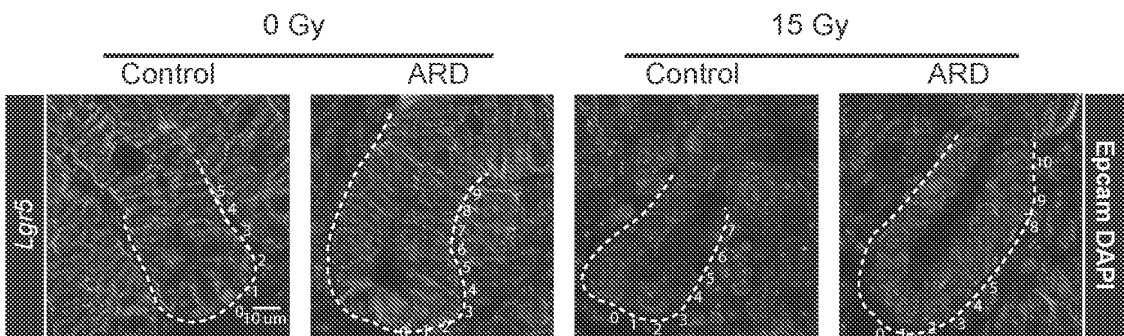


FIG. 4H

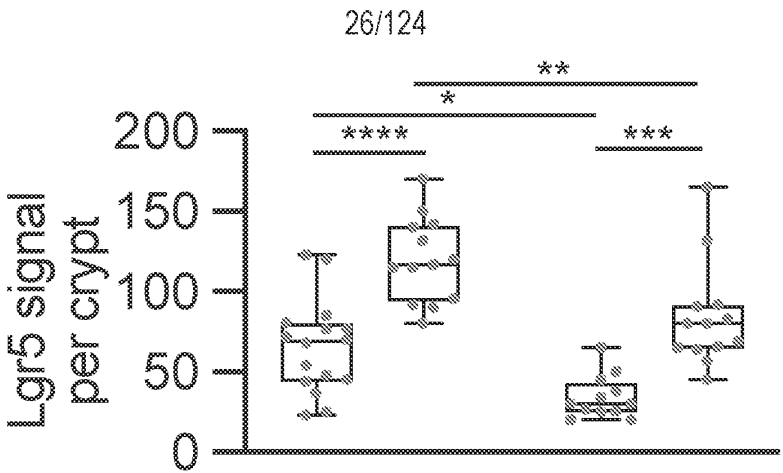


FIG. 4I

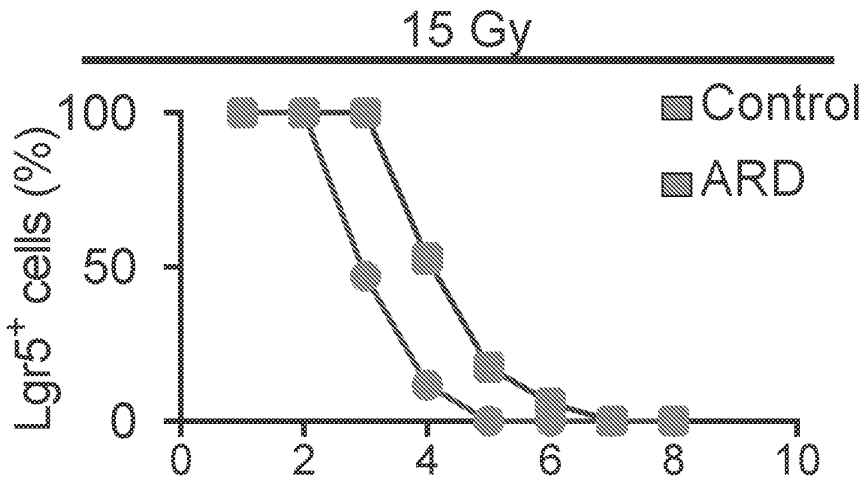


FIG. 4J

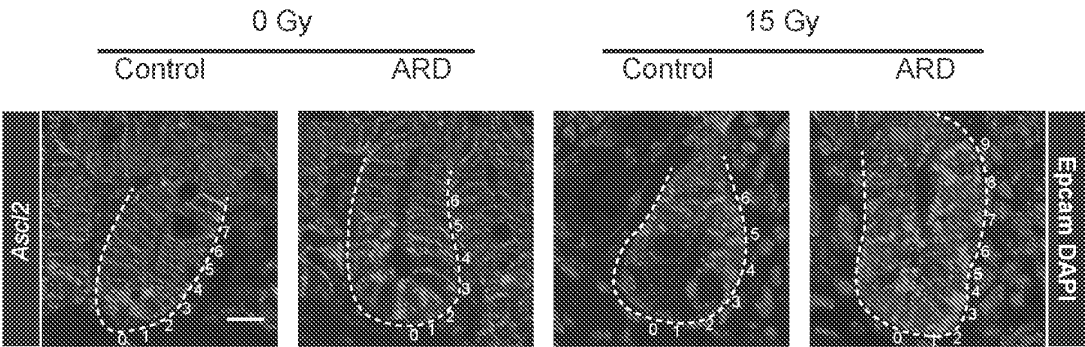


FIG. 4K

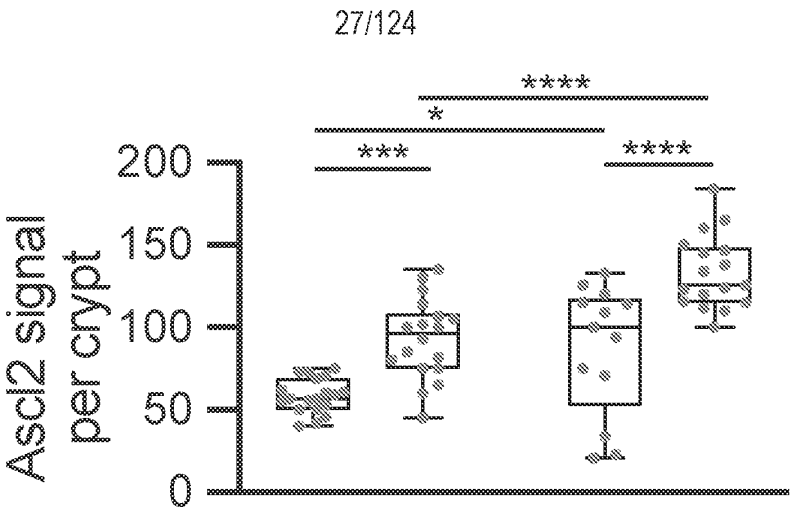


FIG. 4L

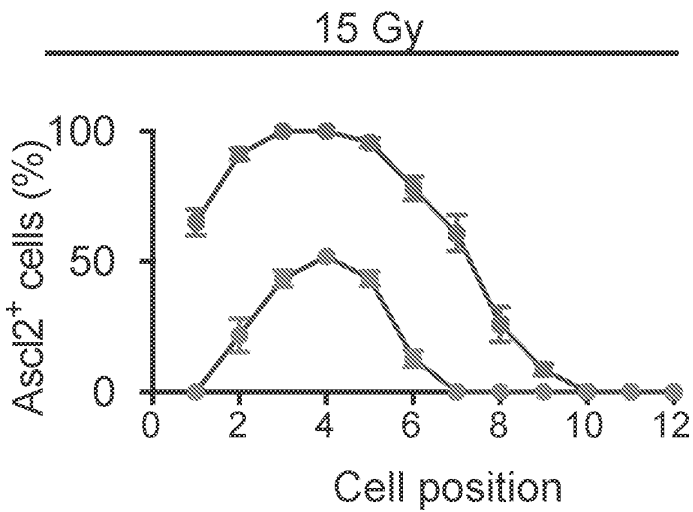


FIG. 4M

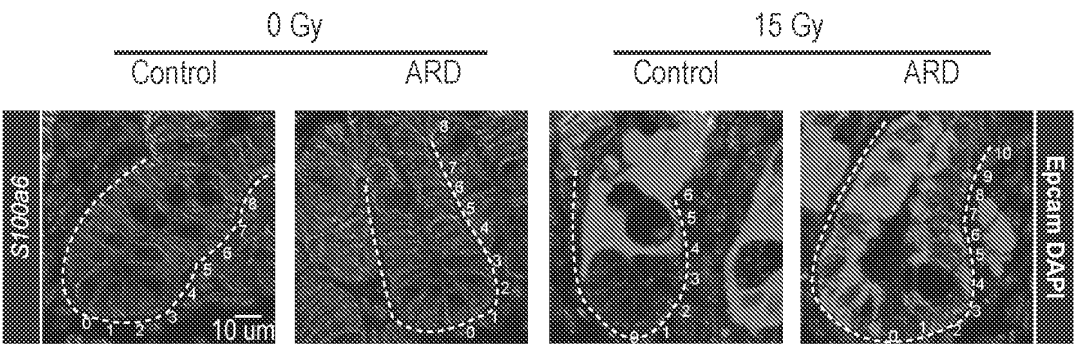


FIG. 4N

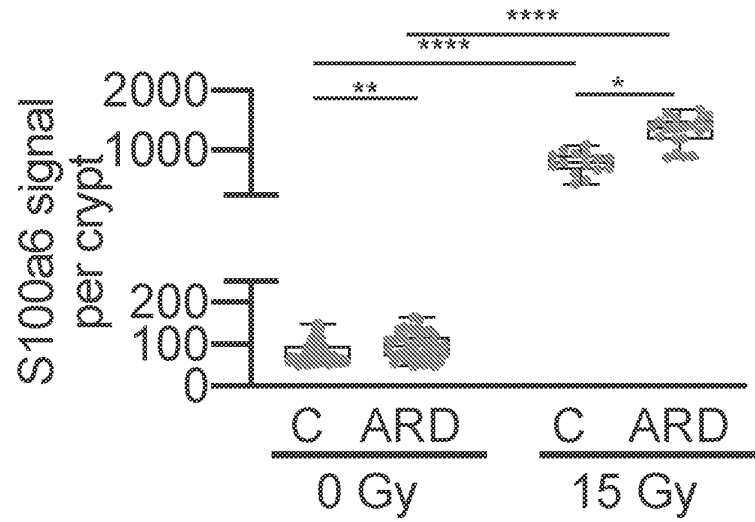


FIG. 4O

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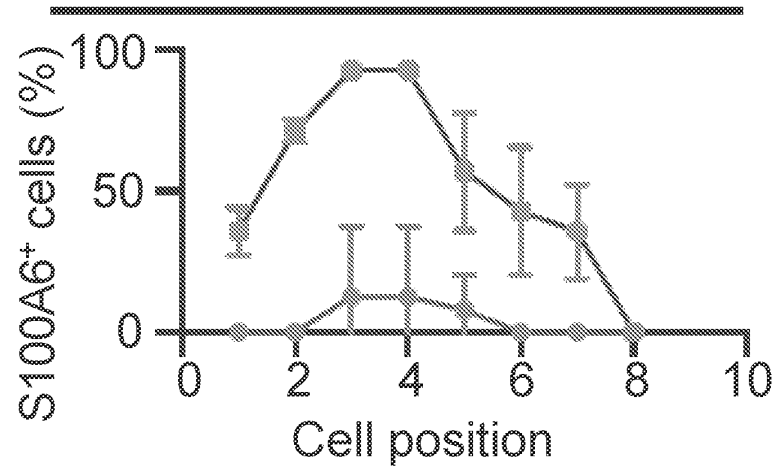


FIG. 4P

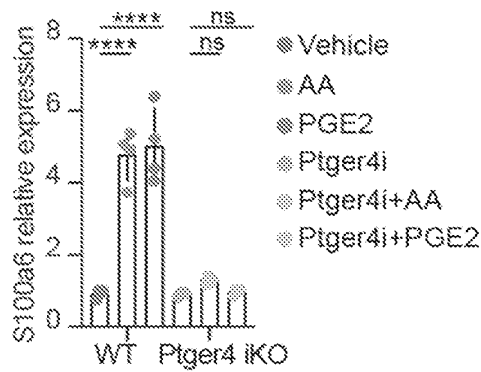


FIG. 4Q

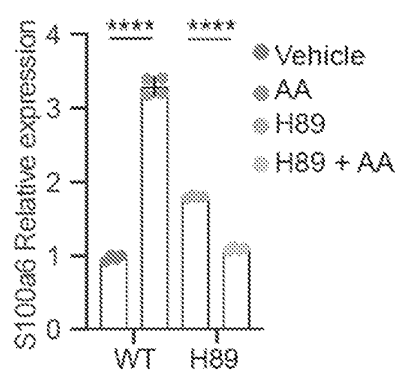


FIG. 4R

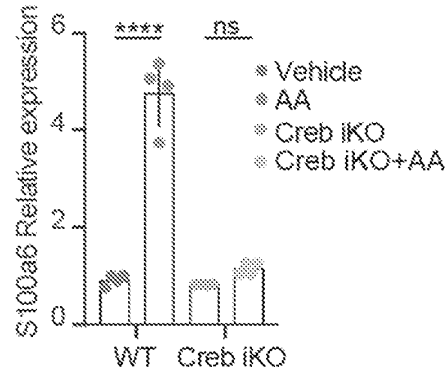


FIG. 4S

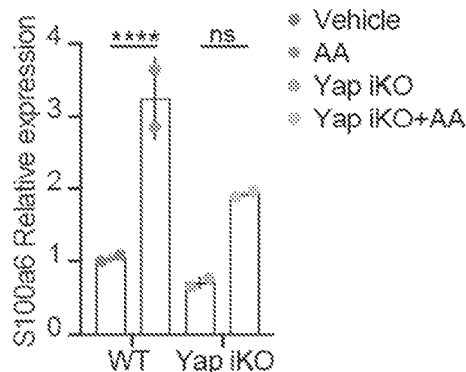


FIG. 4T



FIG. 5A

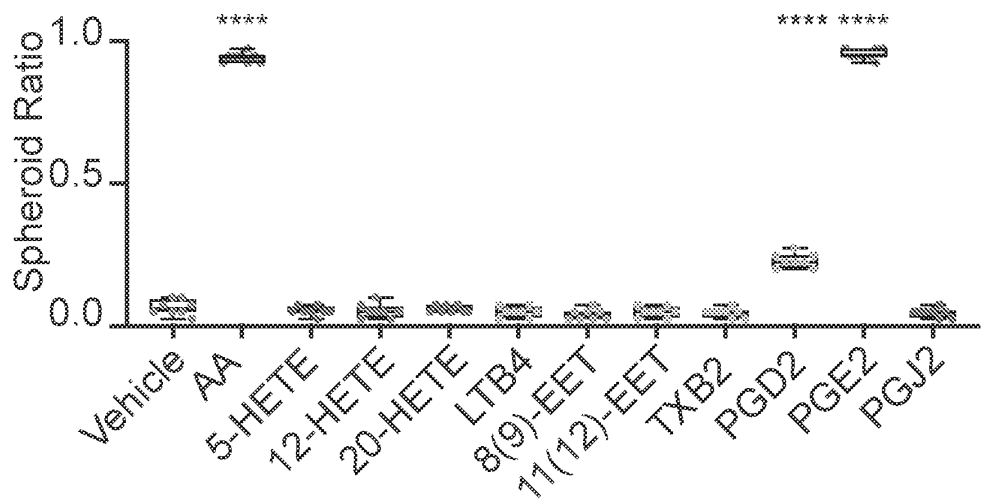


FIG. 5B

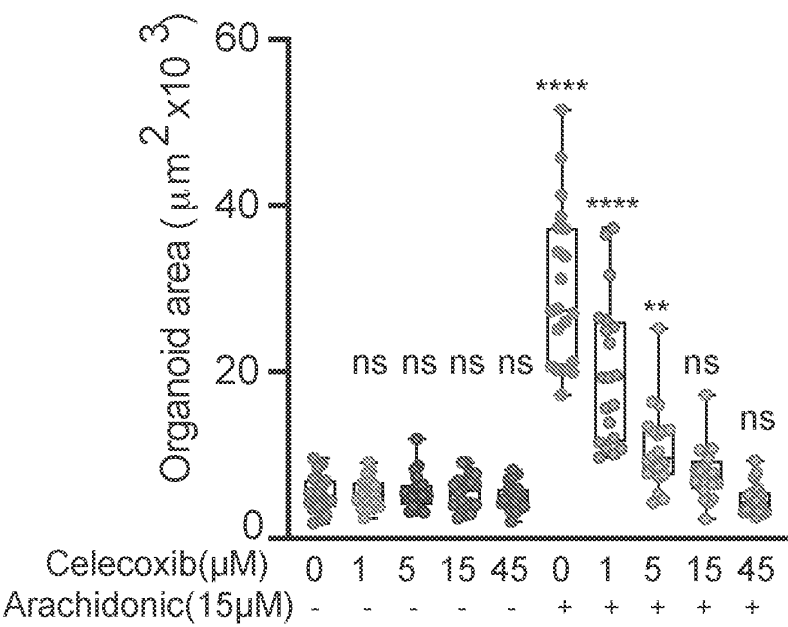


FIG. 5C

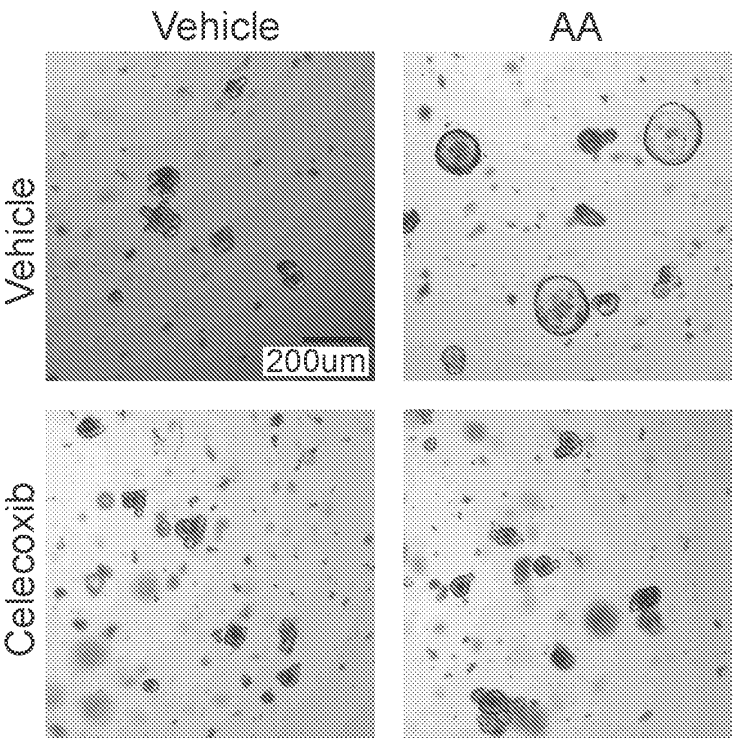


FIG. 5D

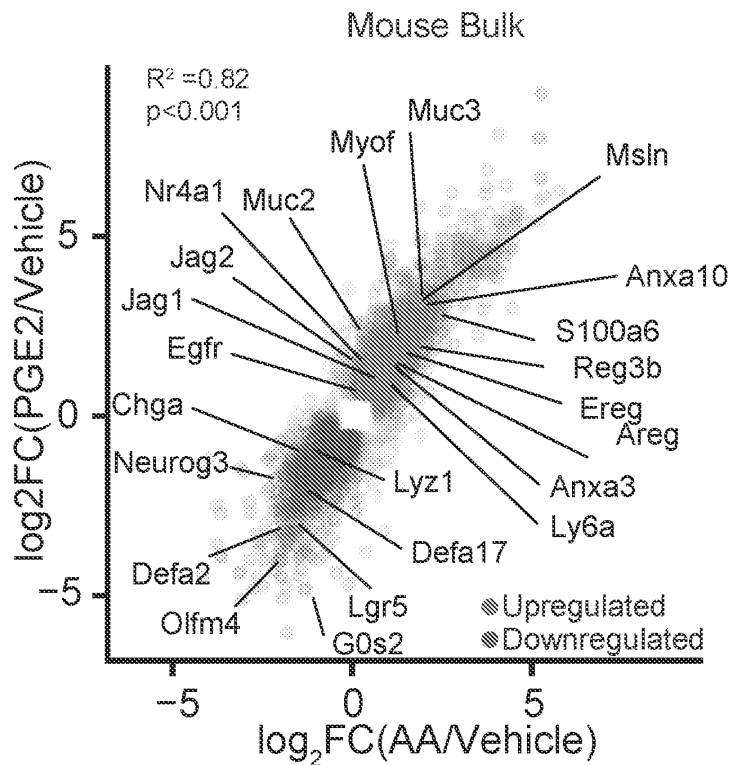


FIG. 5E

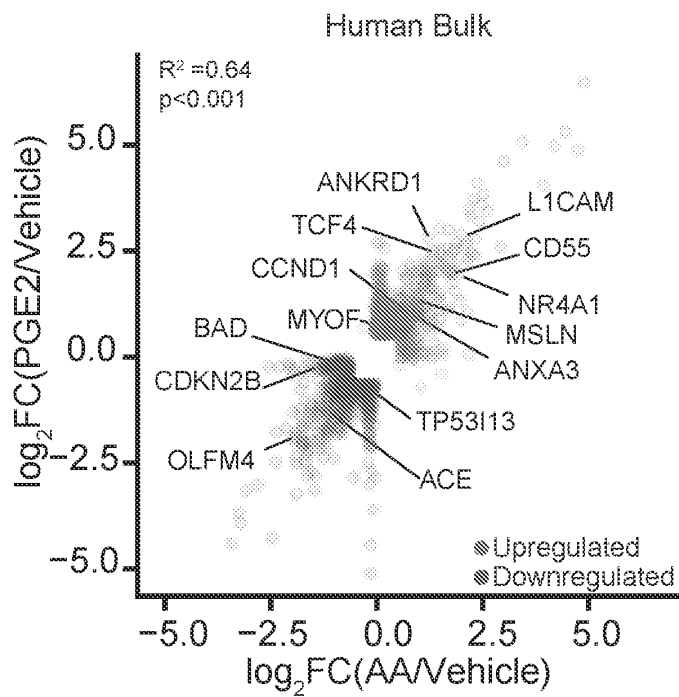


FIG. 5F

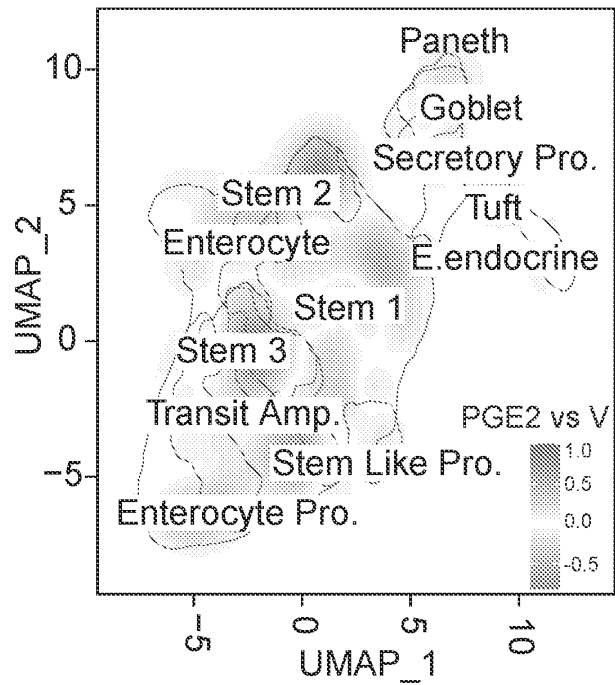


FIG. 5G

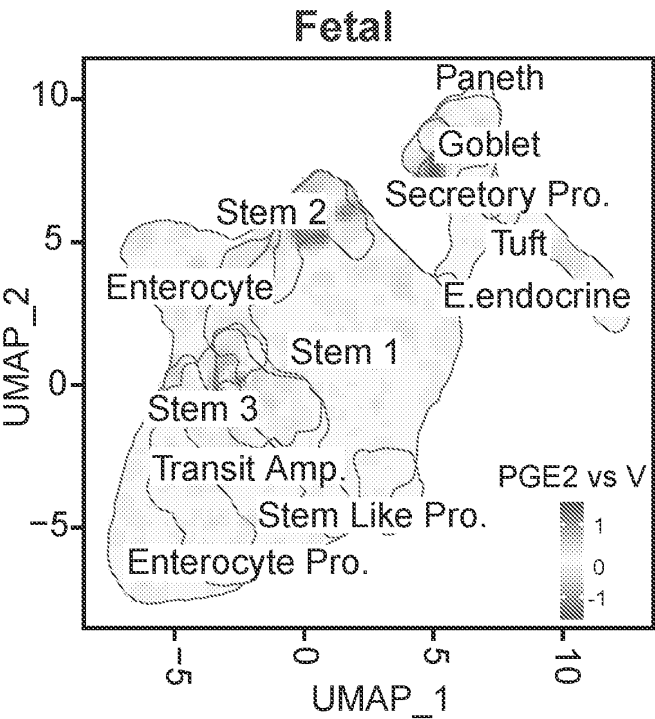


FIG. 5H

●Stem 1 ●Stem 2 ●Stem 3 ●Stem LP ●Secretory Progenitor ●Transit Amplifying
●Enterocyte Progenitor ●Enterocyte ●Enteroendocrine ●Goblet ●Tuft ●Paneth

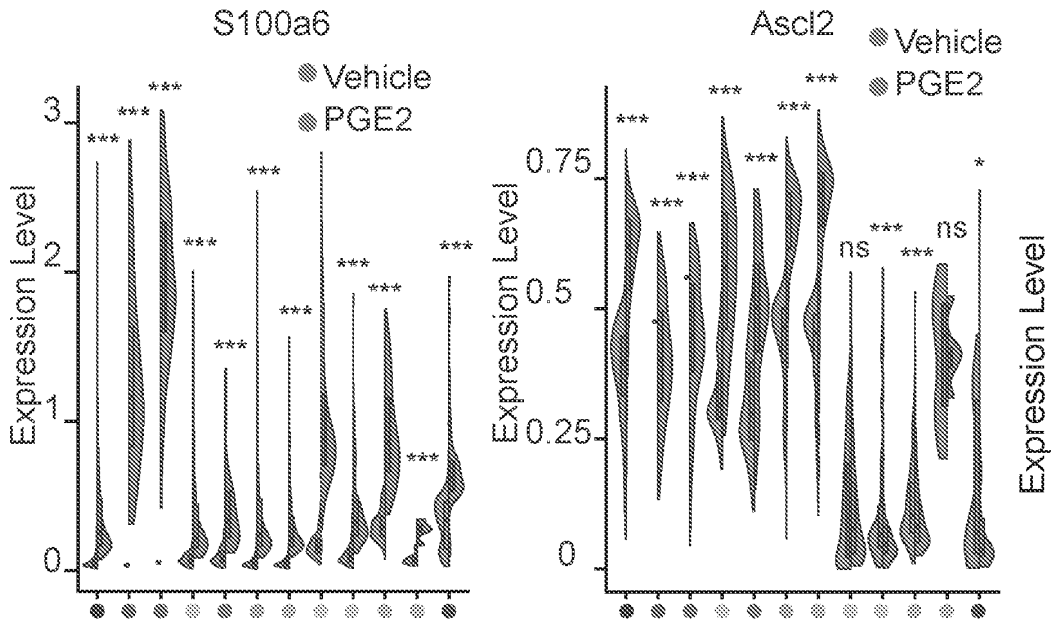


FIG. 5I

FIG. 5J

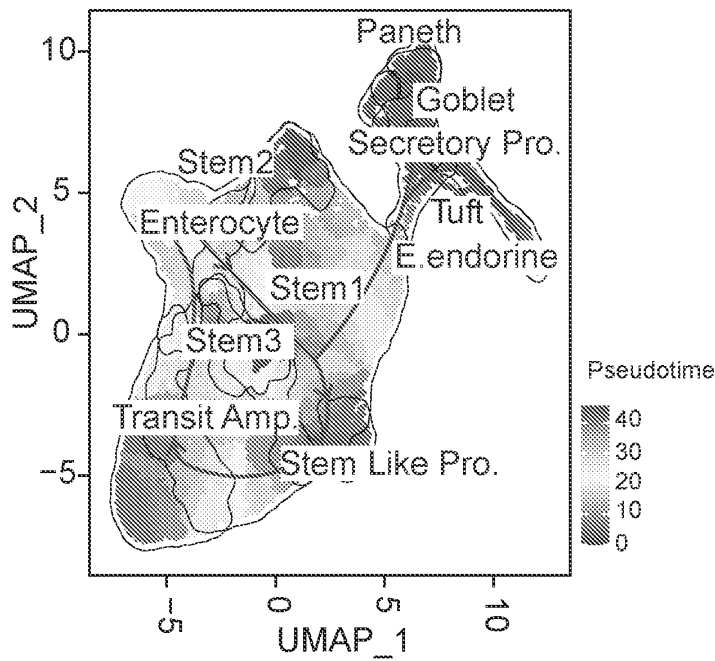


FIG. 5K

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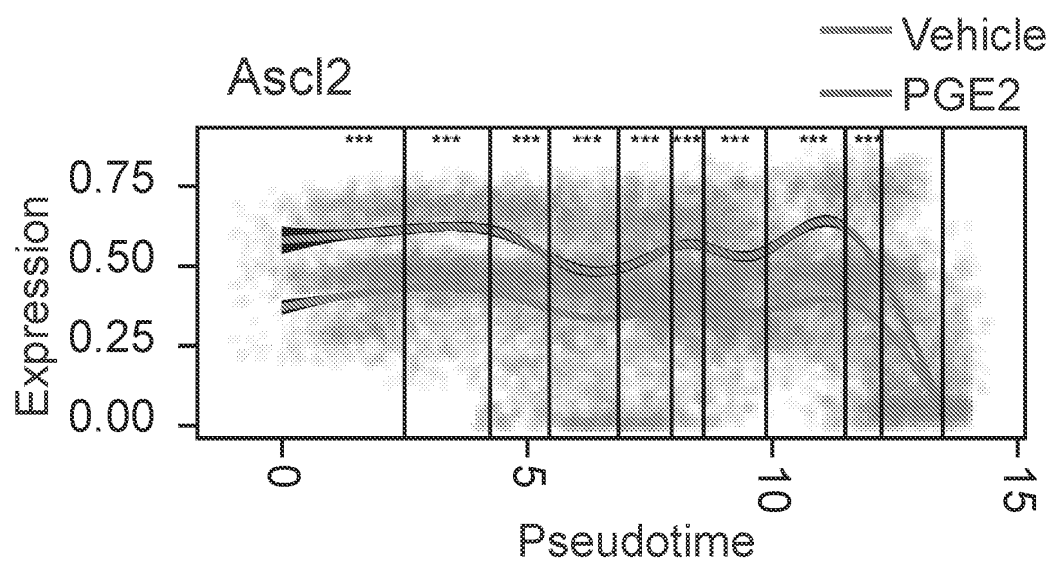


FIG. 5L

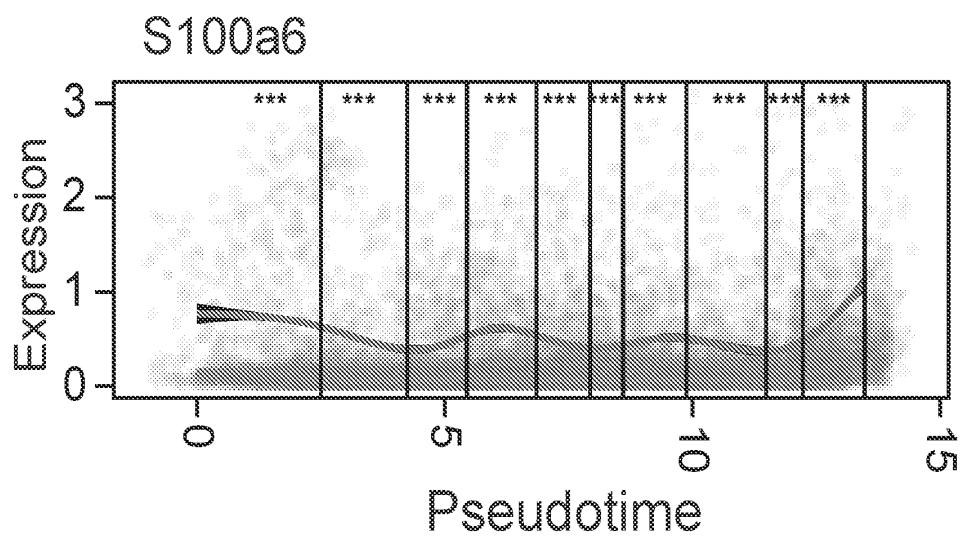


FIG. 5M

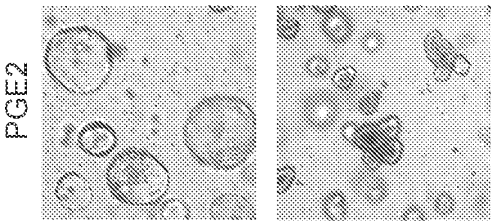
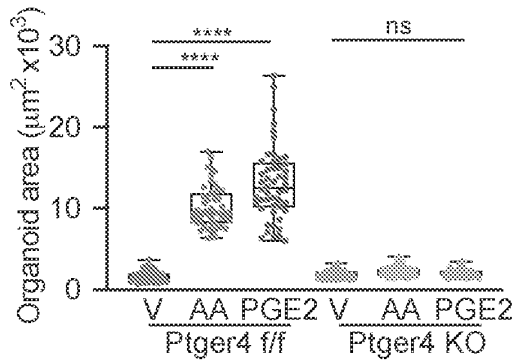
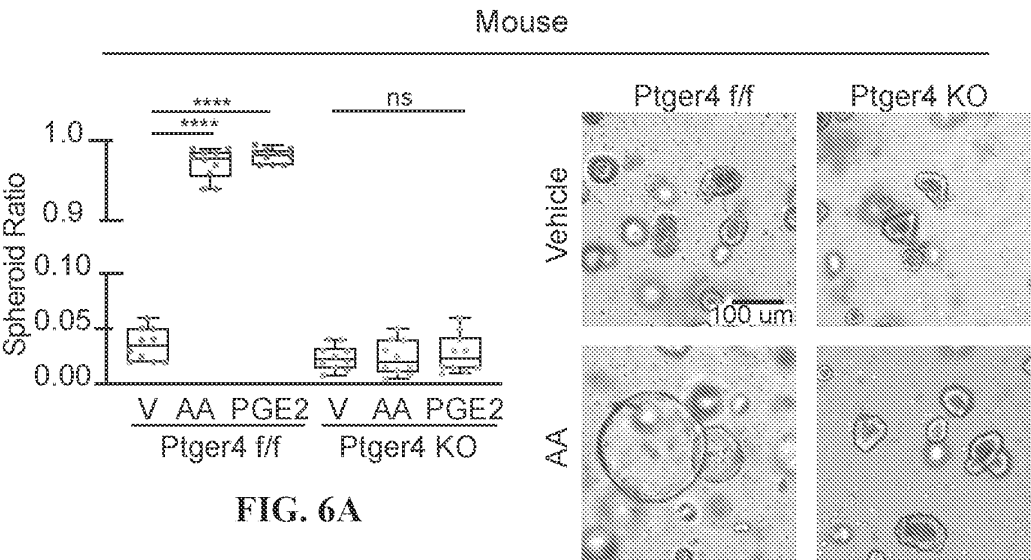


FIG. 6B

FIG. 6C

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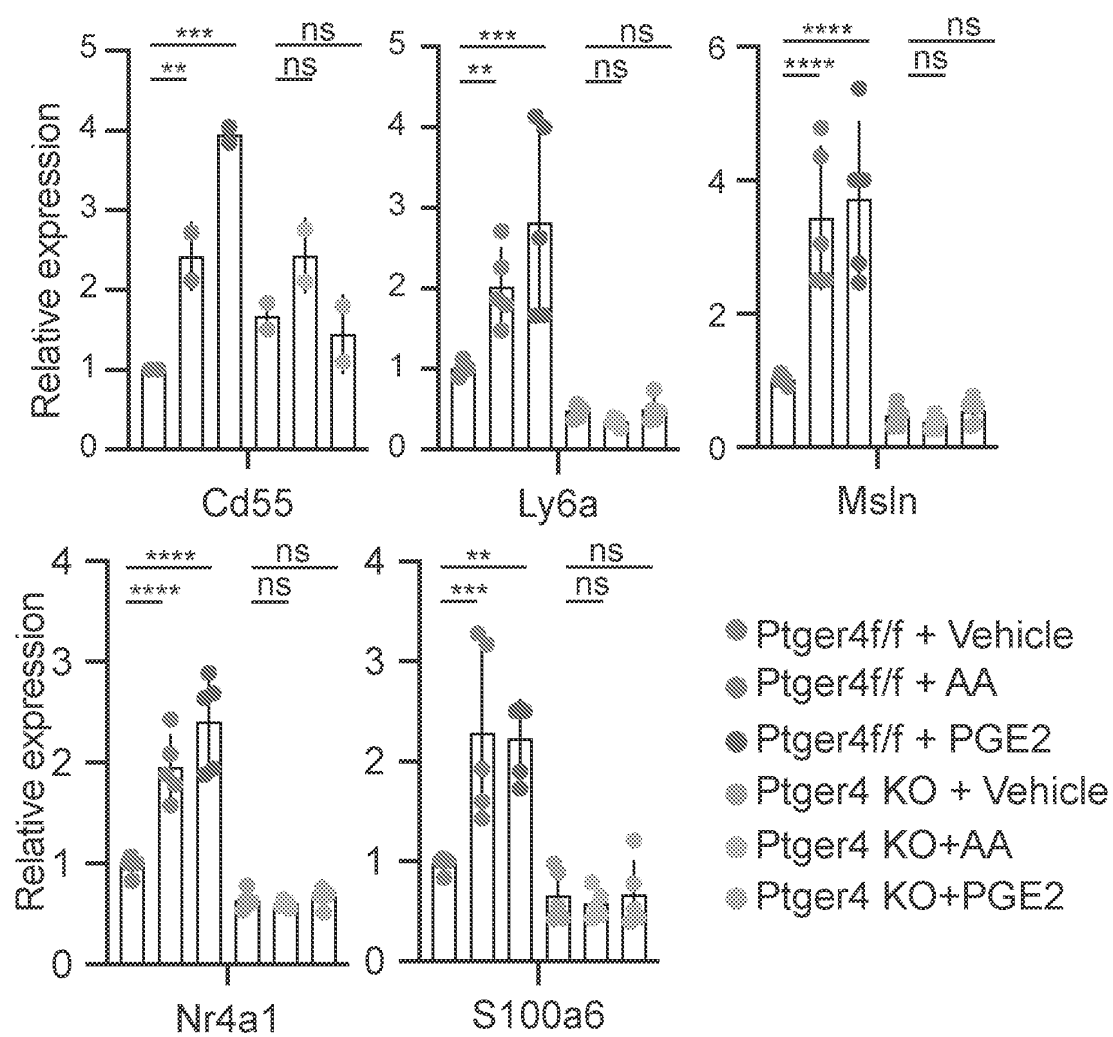


FIG. 6D

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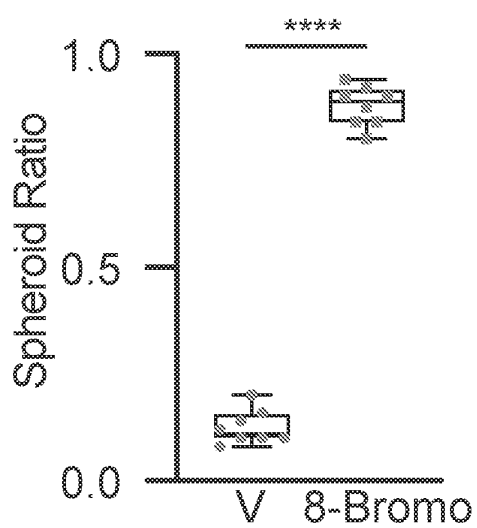


FIG. 6E

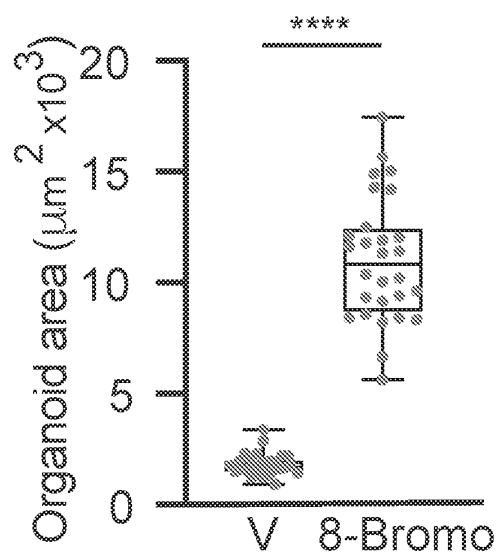


FIG. 6F

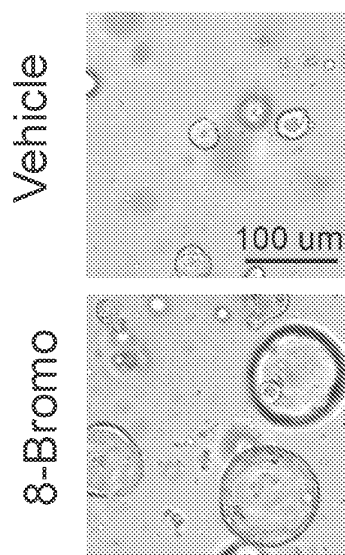


FIG. 6G

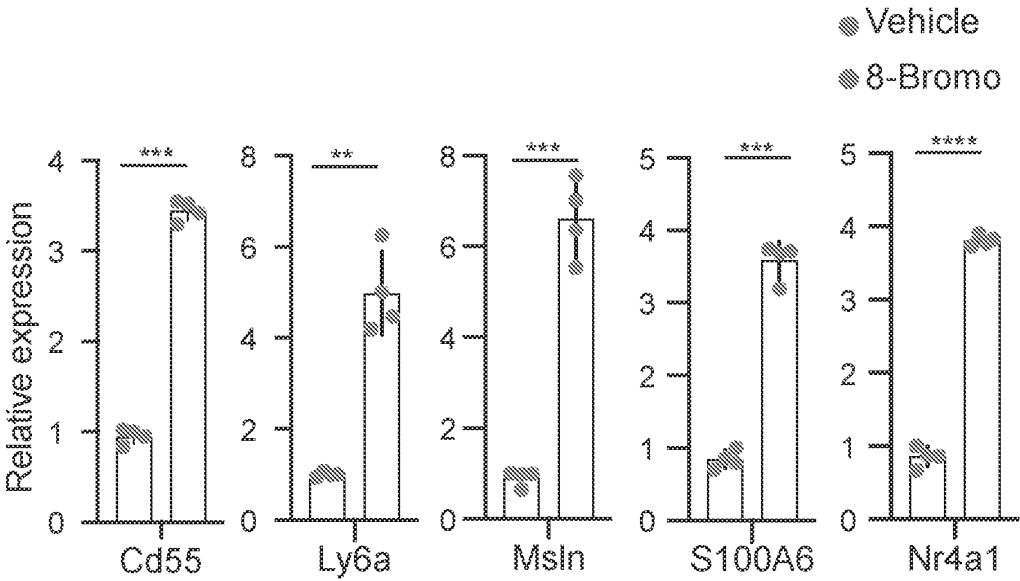


FIG. 6H

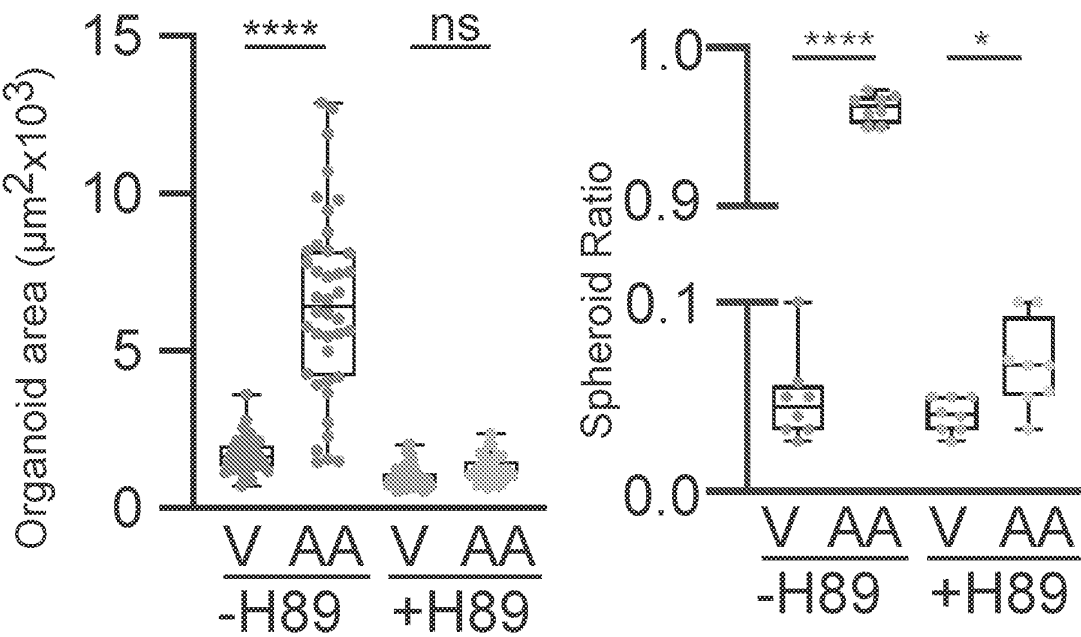


FIG. 6I

FIG. 6J

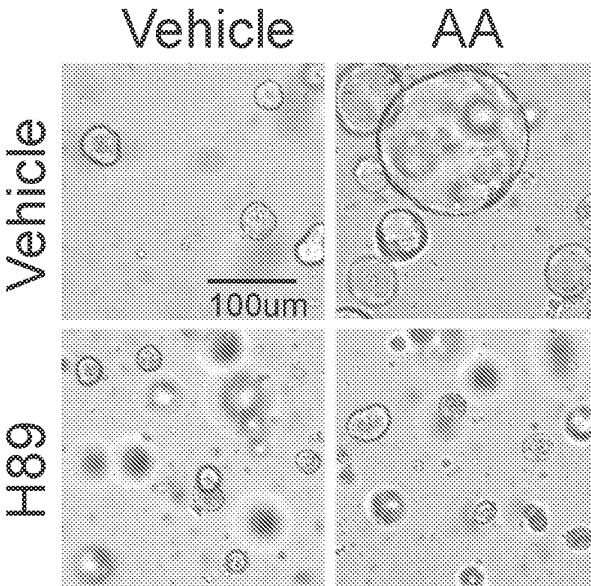


FIG. 6K

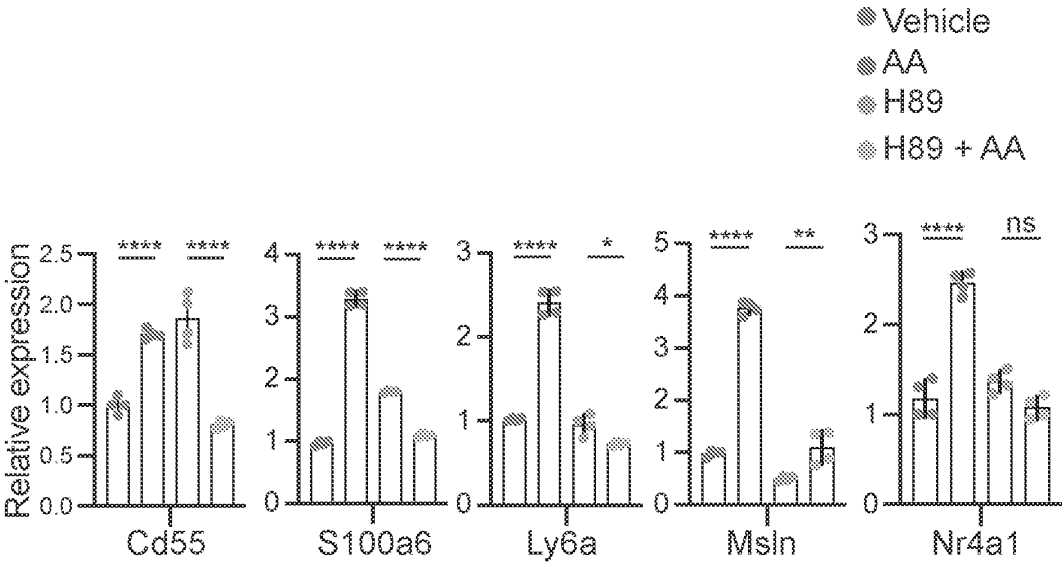


FIG. 6L

Human

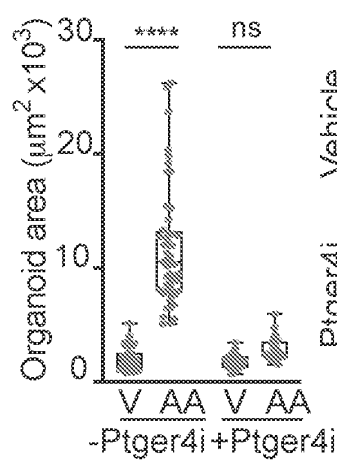


FIG. 6M

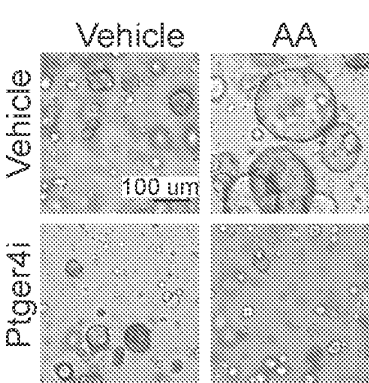


FIG. 6N

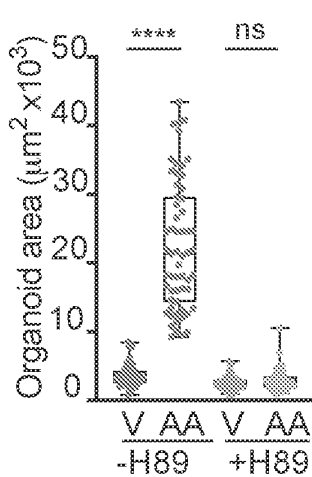


FIG. 6O

Human

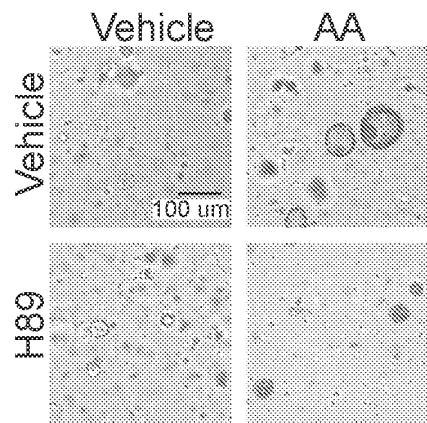


FIG. 6P

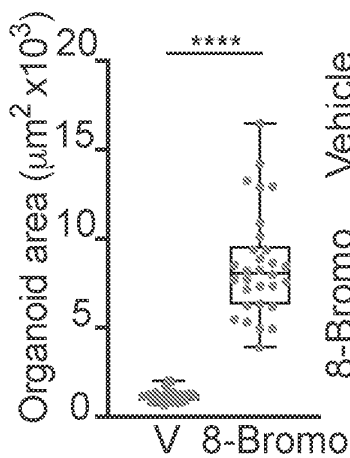


FIG. 6Q

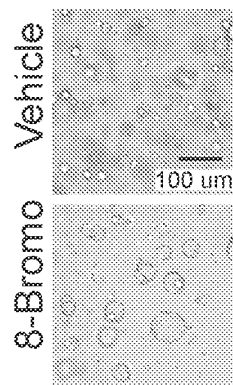


FIG. 6R

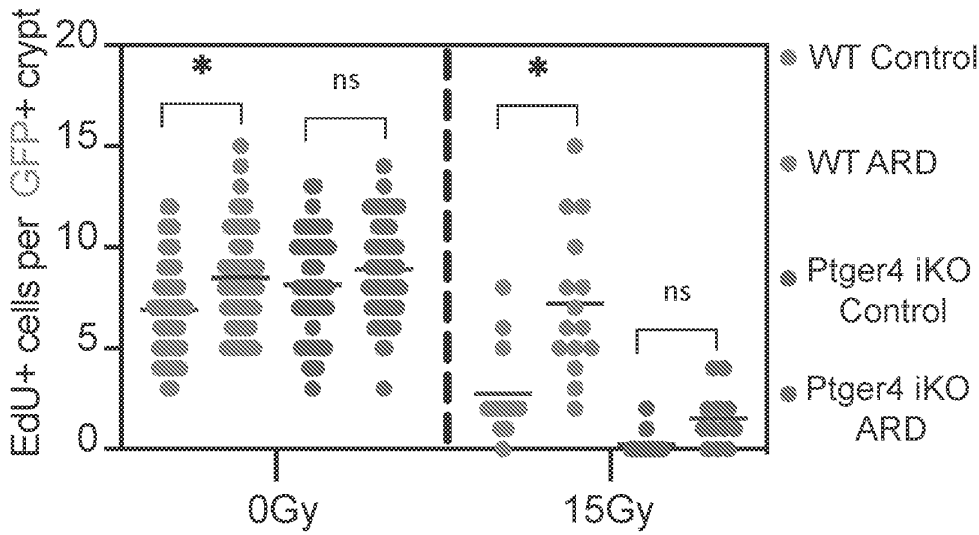


FIG. 6S

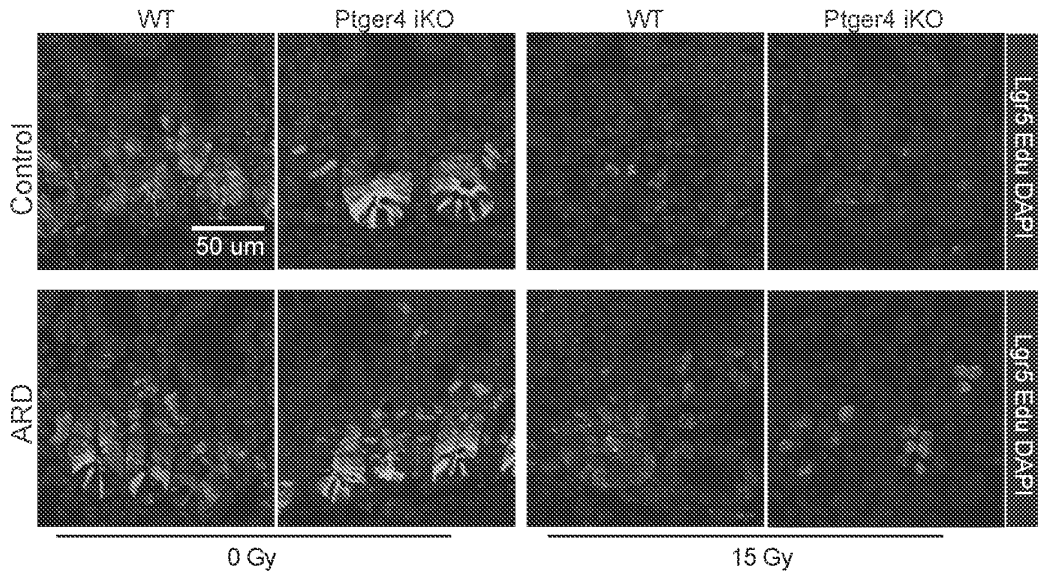
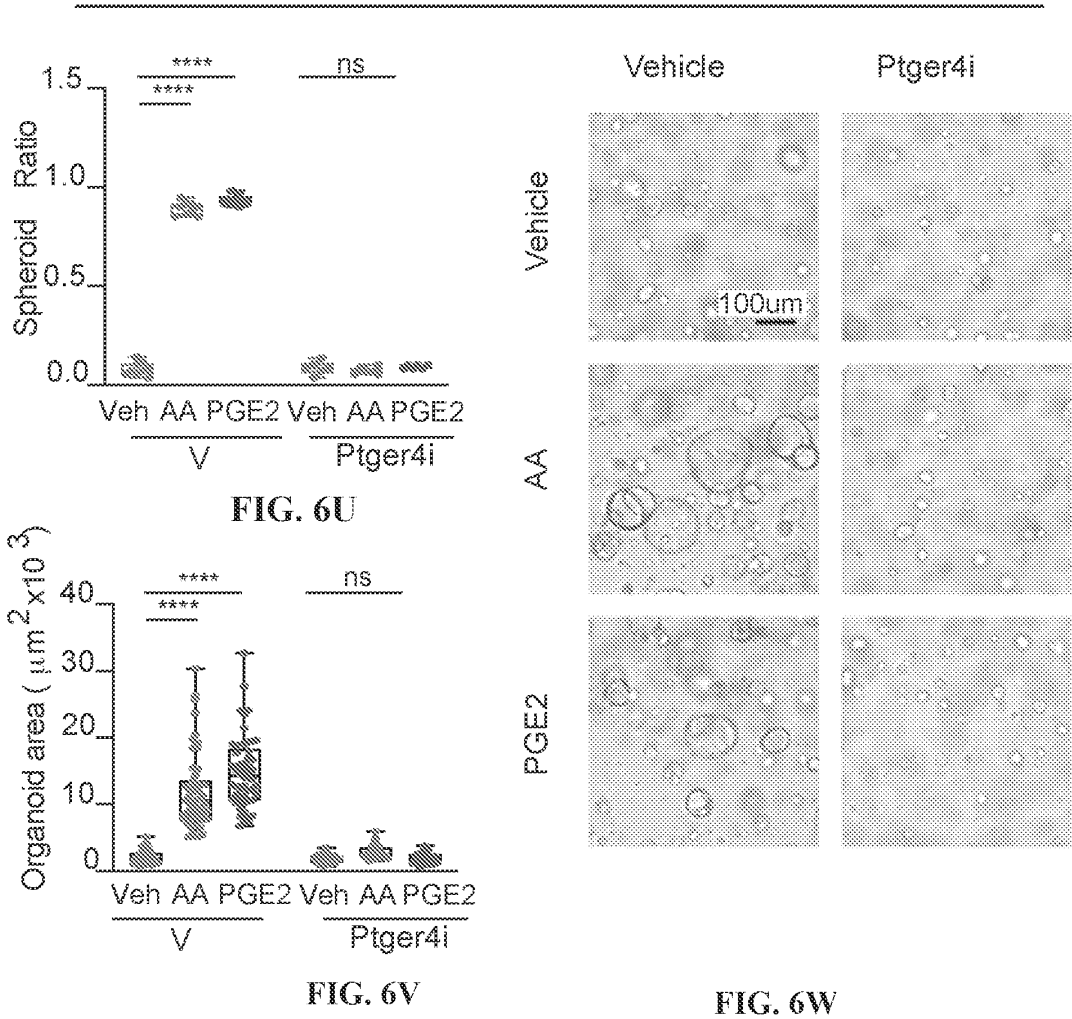


FIG. 6T

Human



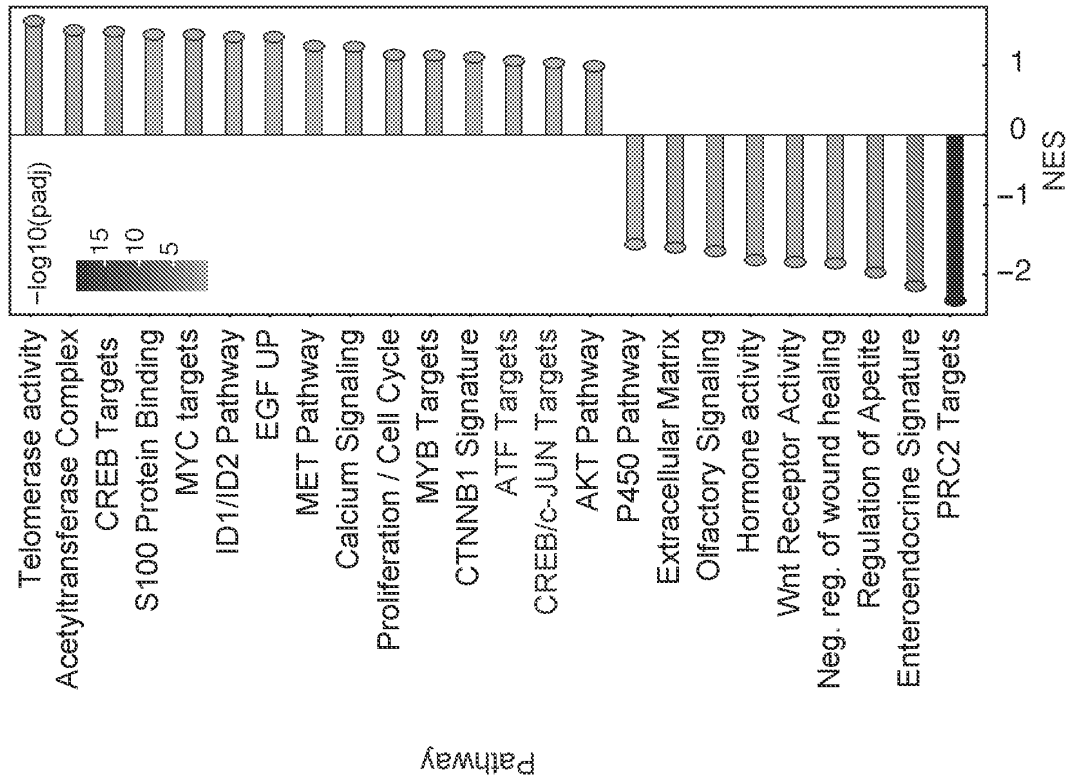


FIG. 7A

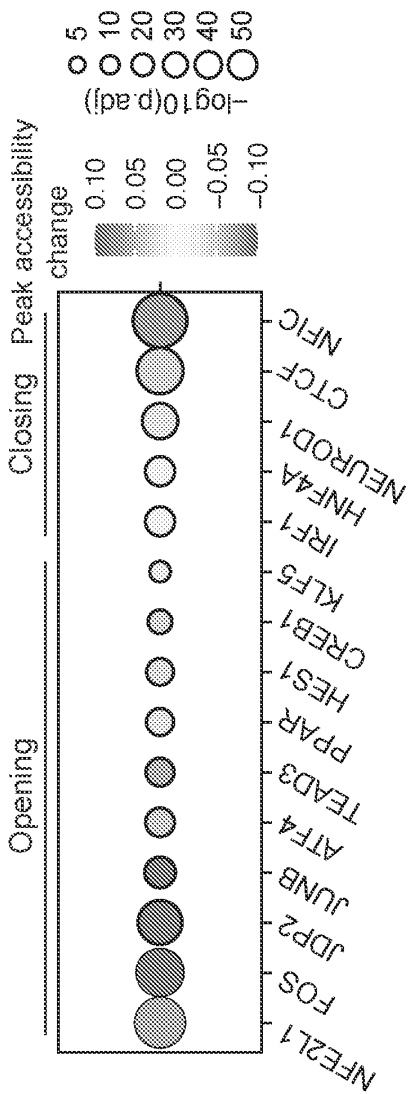


FIG. 7B

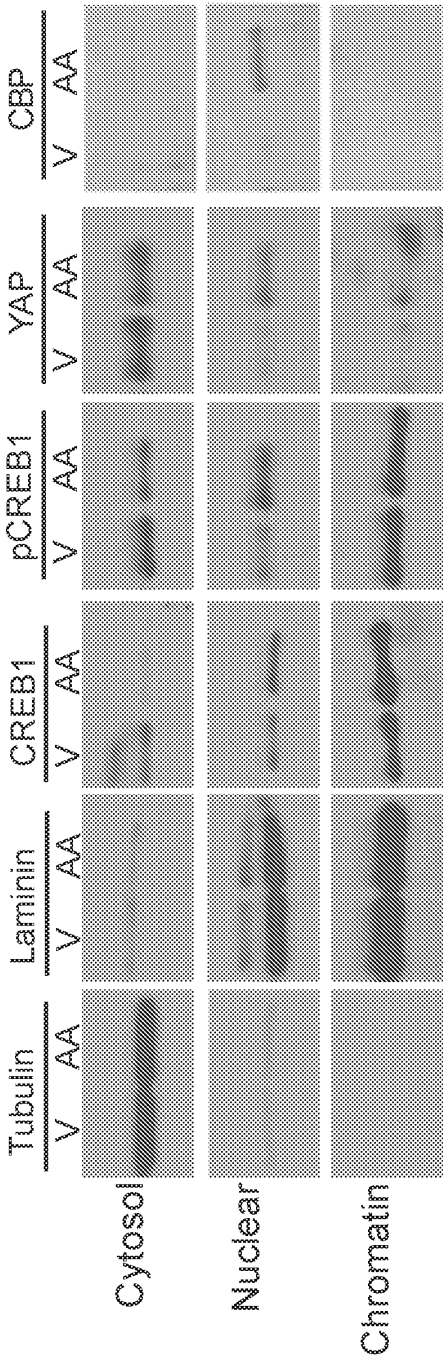
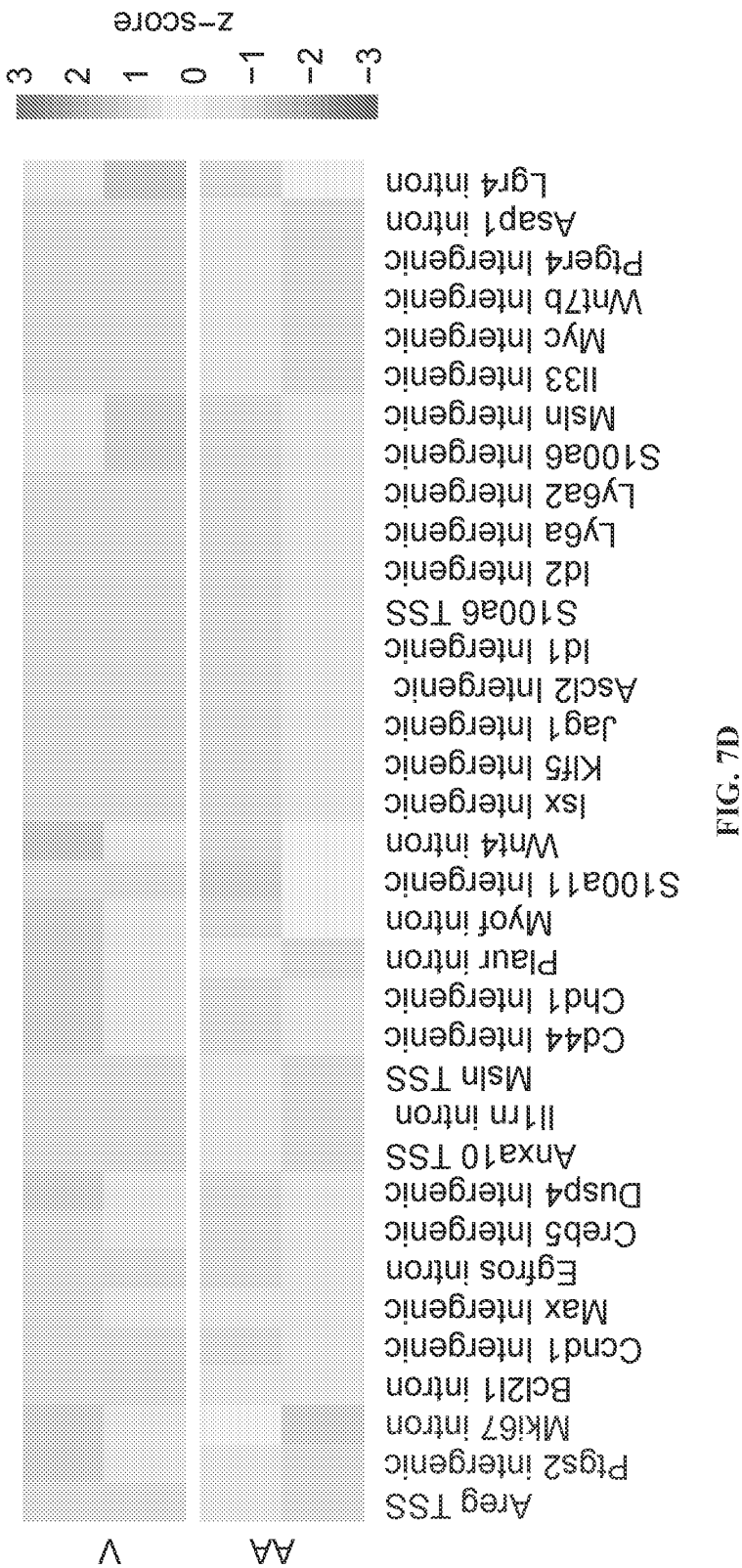


FIG. 7C



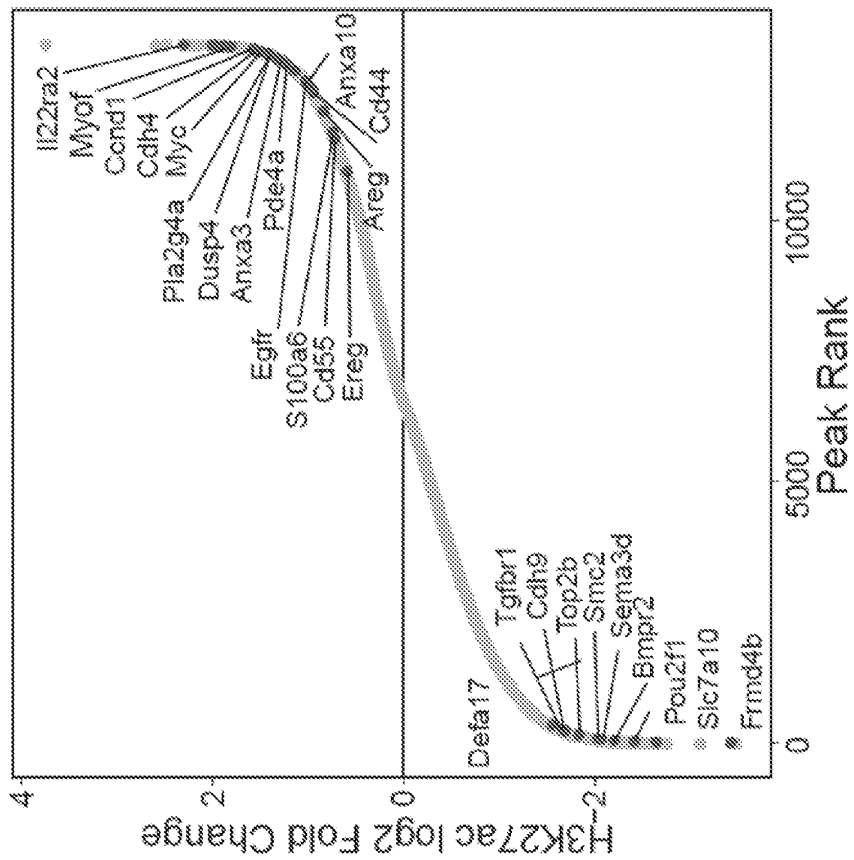


FIG. 7F

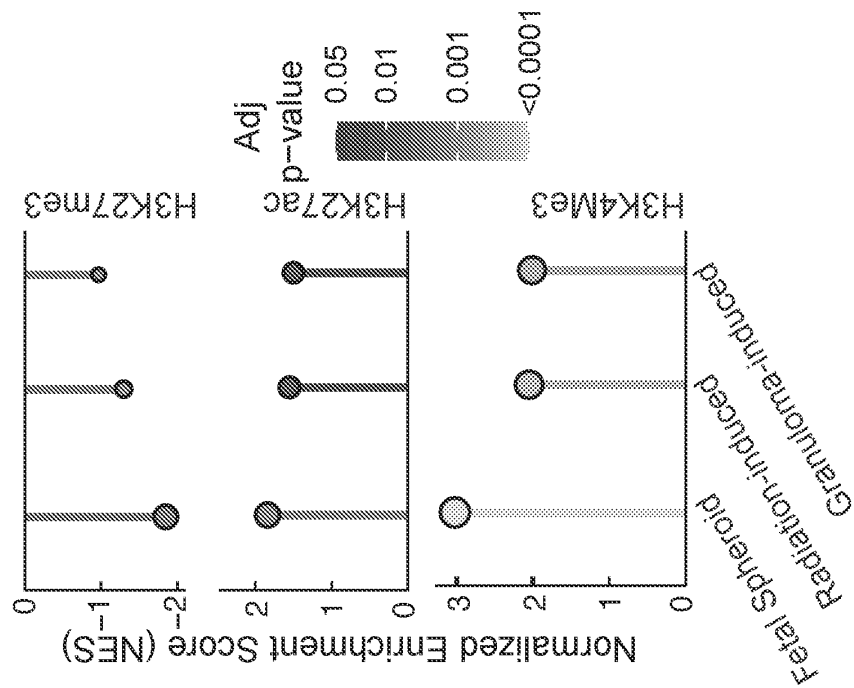


FIG. 7E

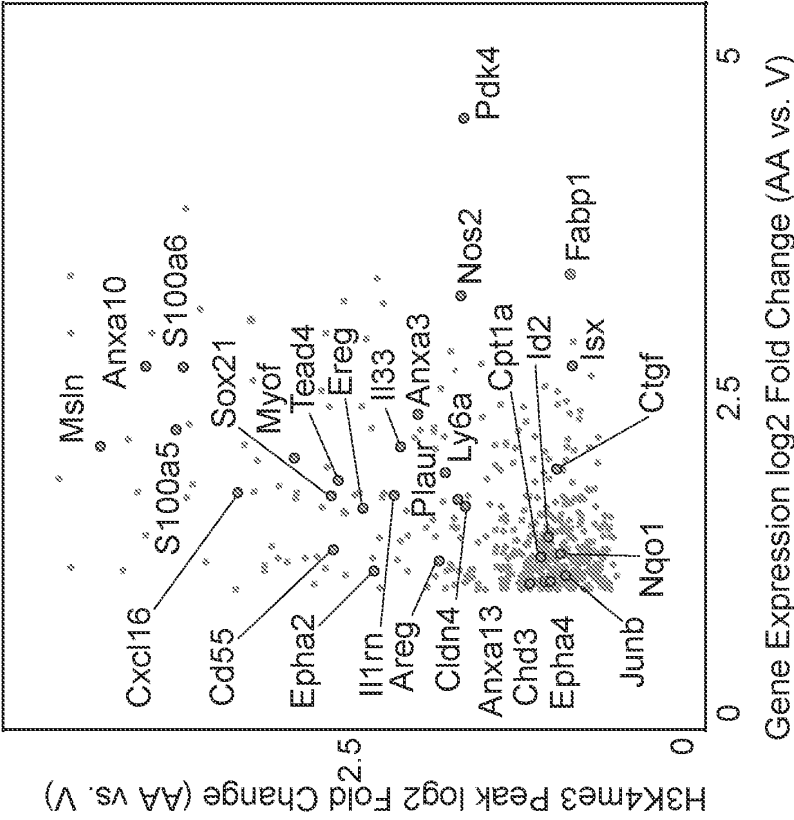


FIG. 7G

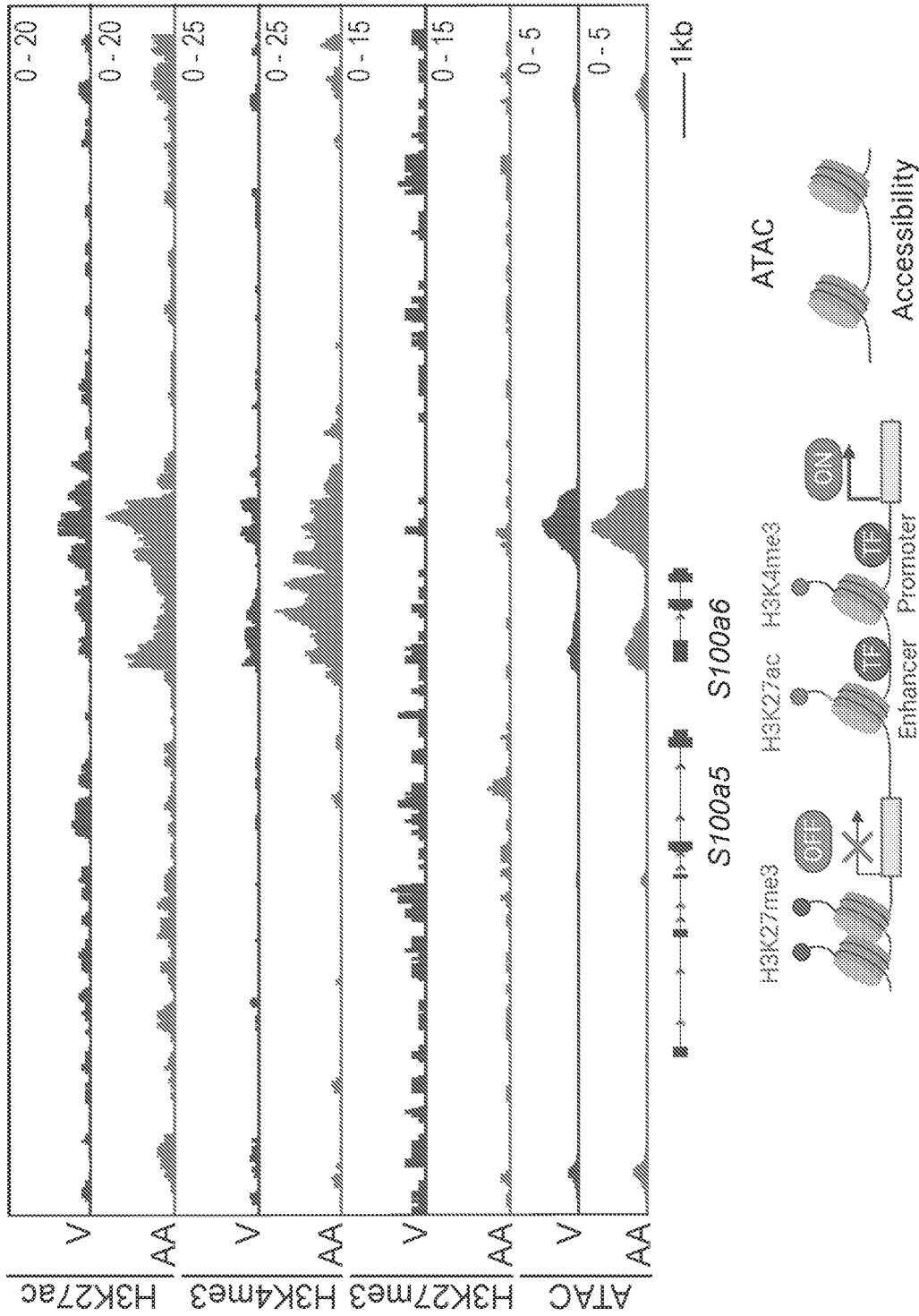


FIG. 7H

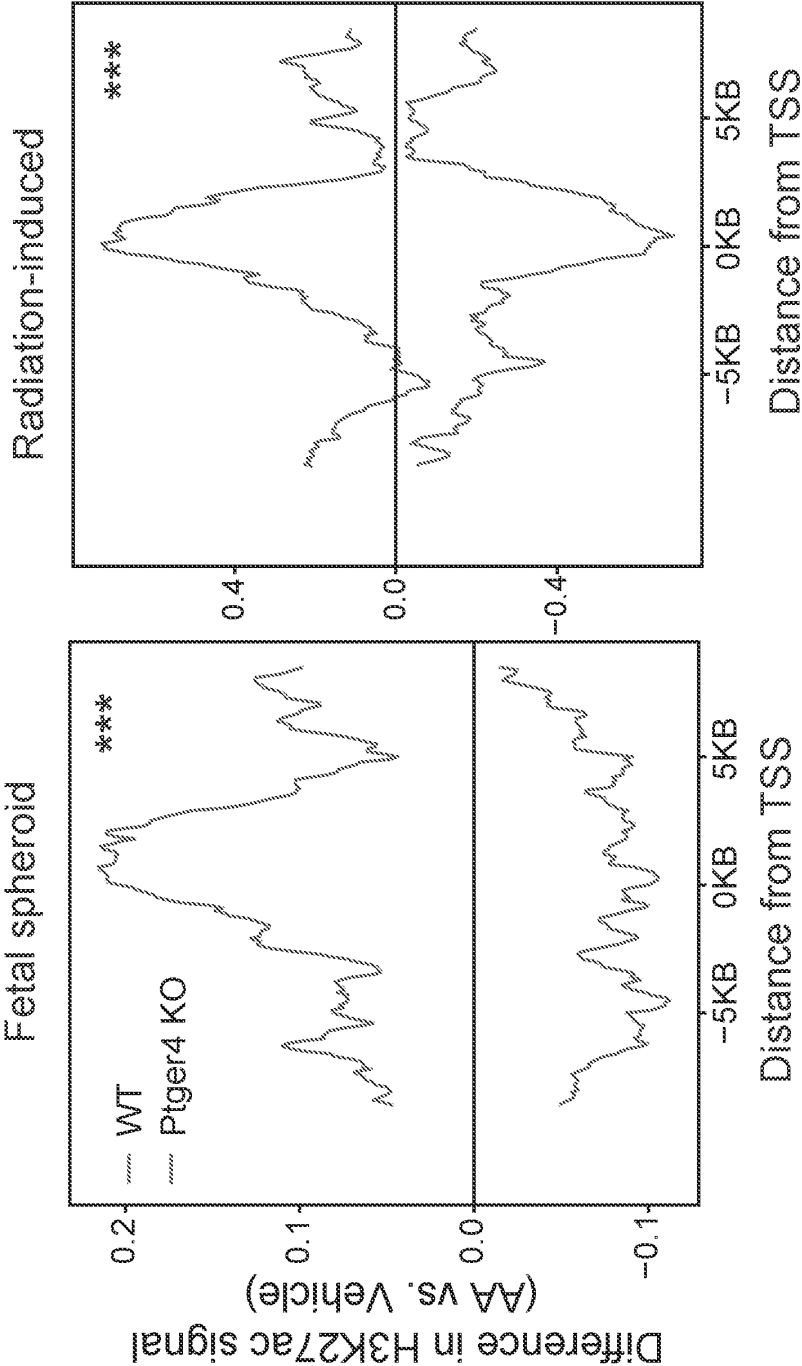


FIG. 7I

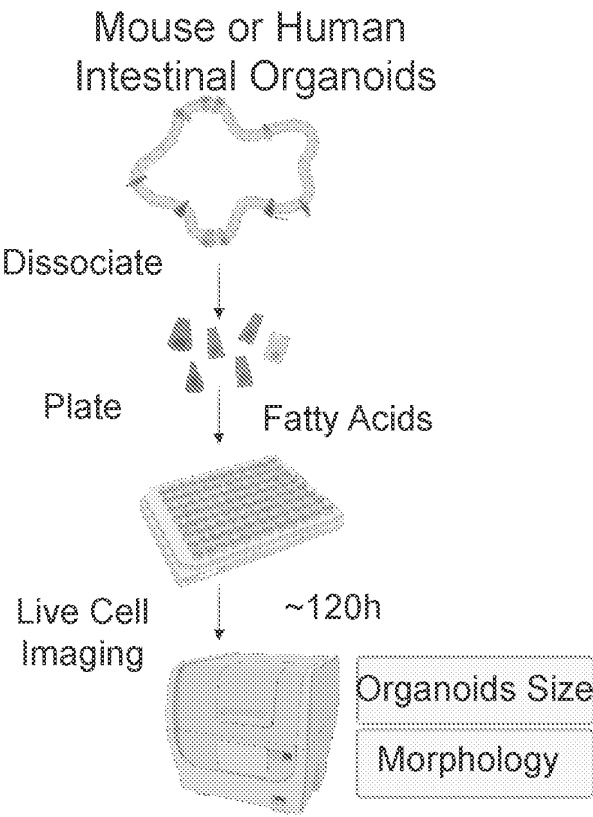


FIG. 8A

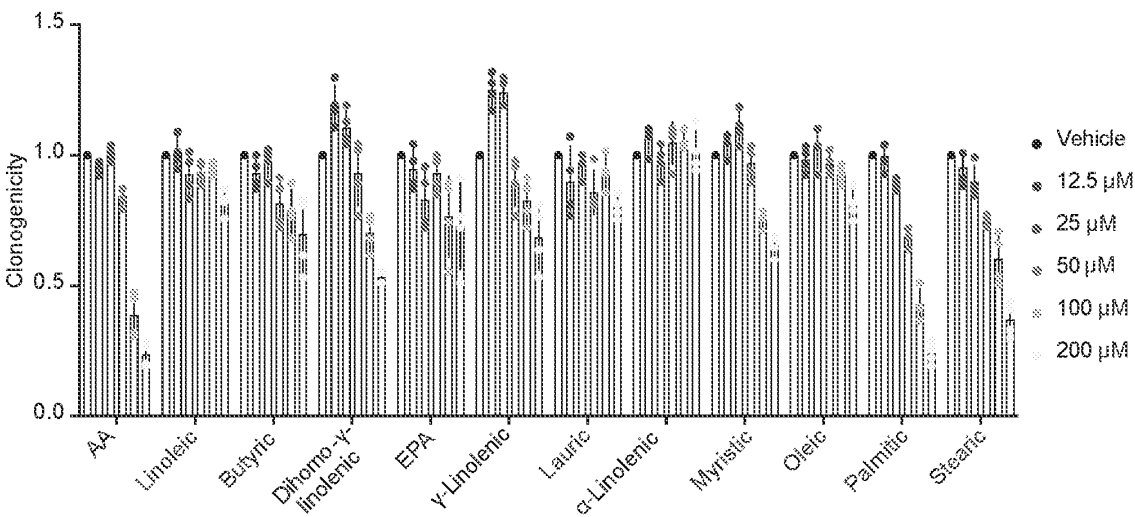


FIG. 8B

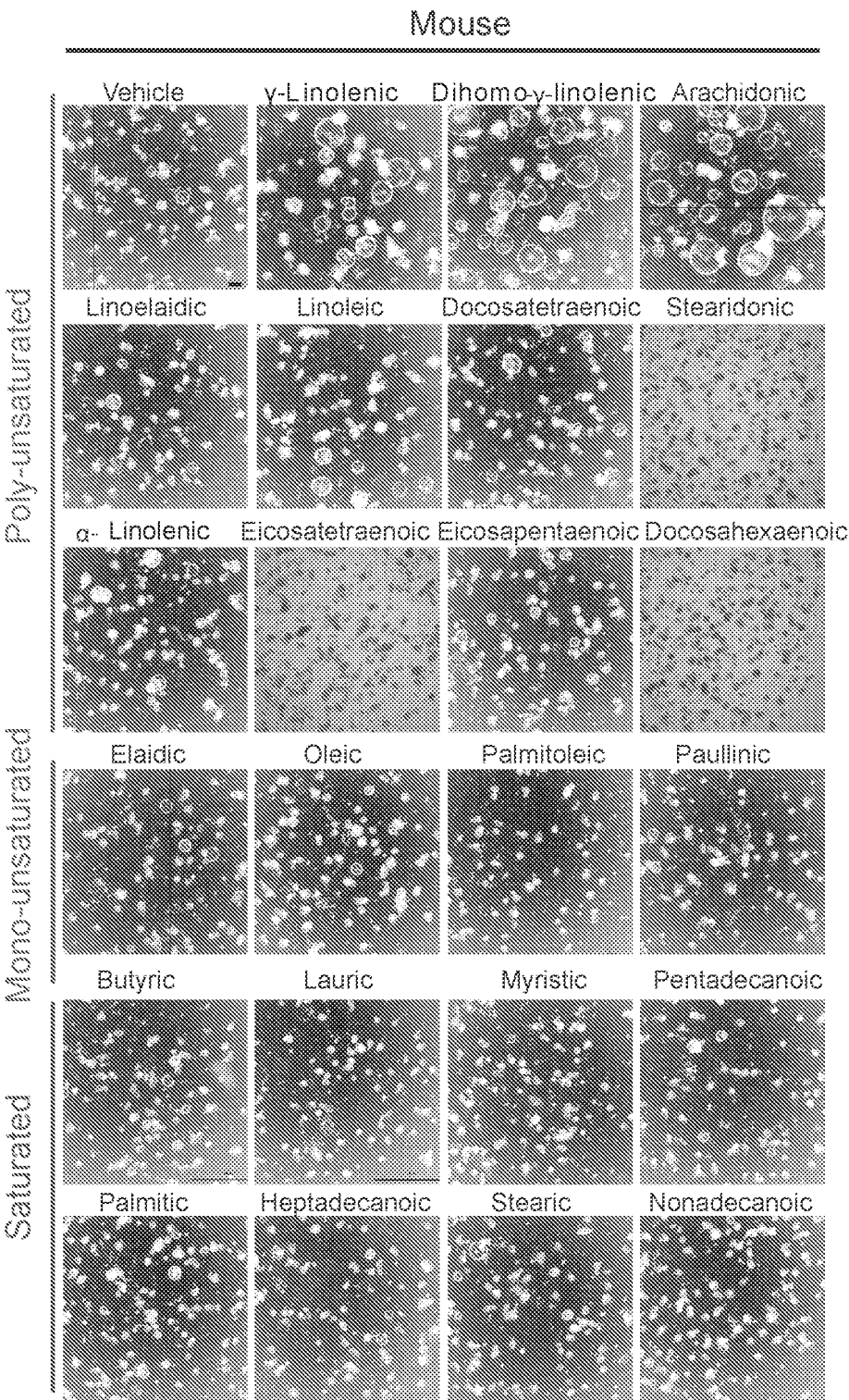


FIG. 8C

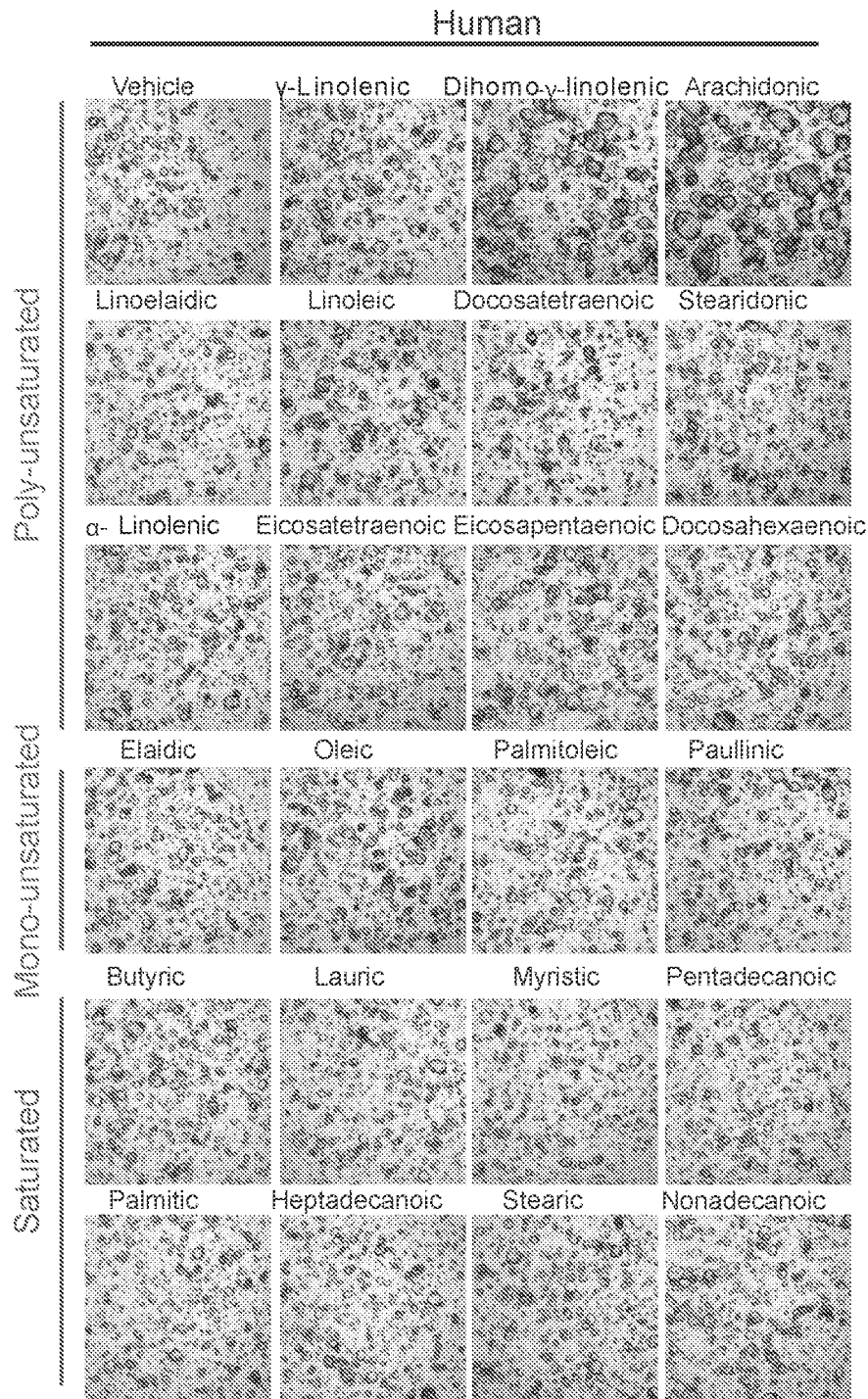


FIG. 8D

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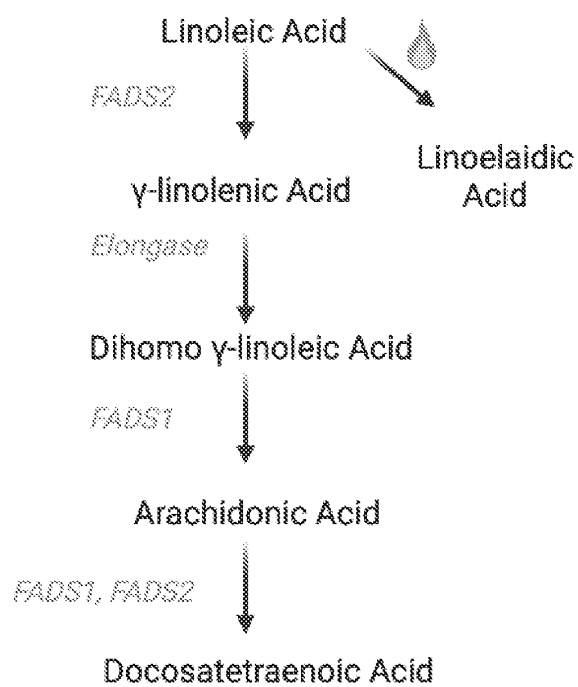


FIG. 8E

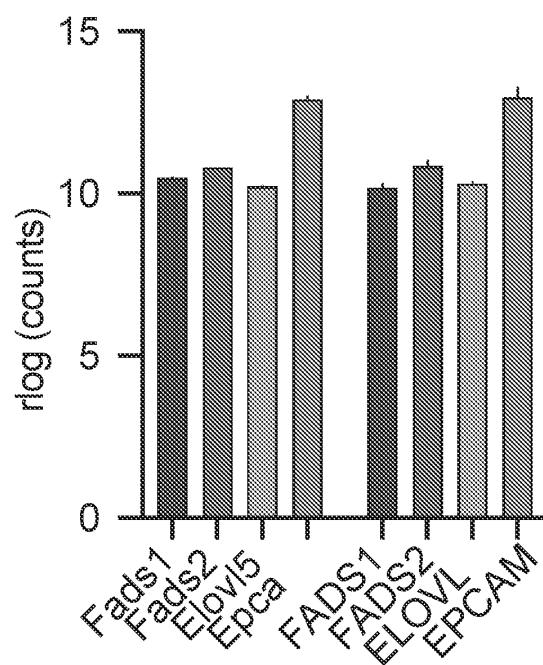


FIG. 8F

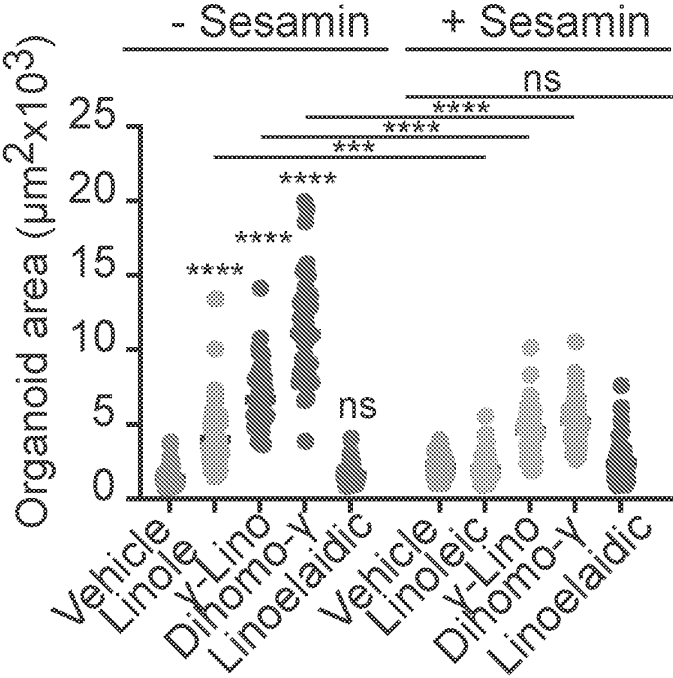


FIG. 8G

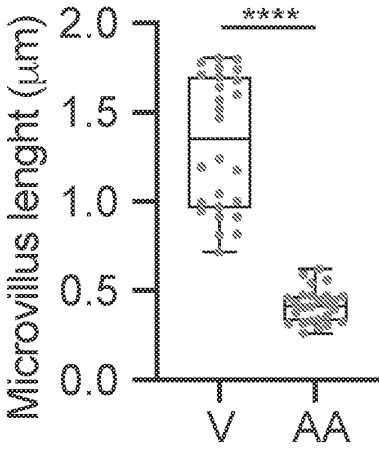


FIG. 8H

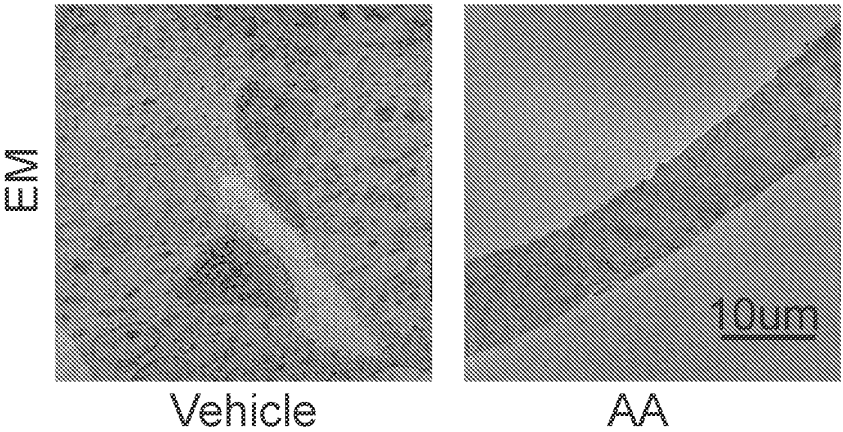


FIG. 8I

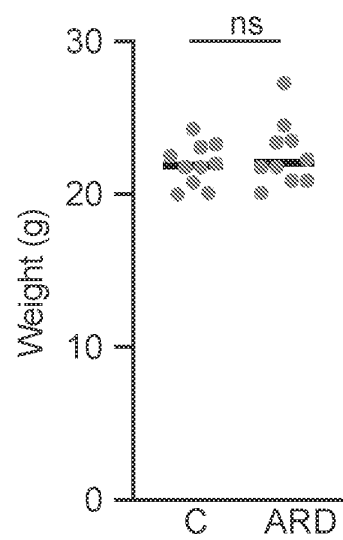


FIG. 9A

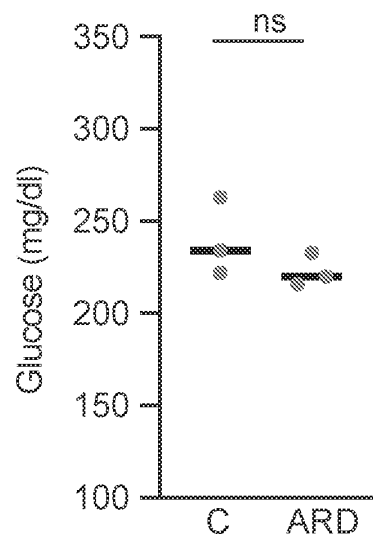


FIG. 9B

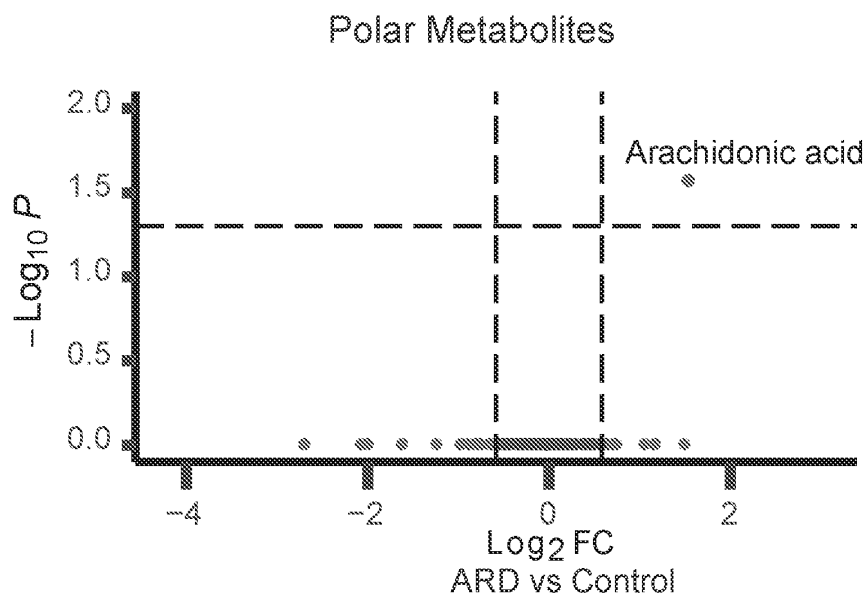


FIG. 9C

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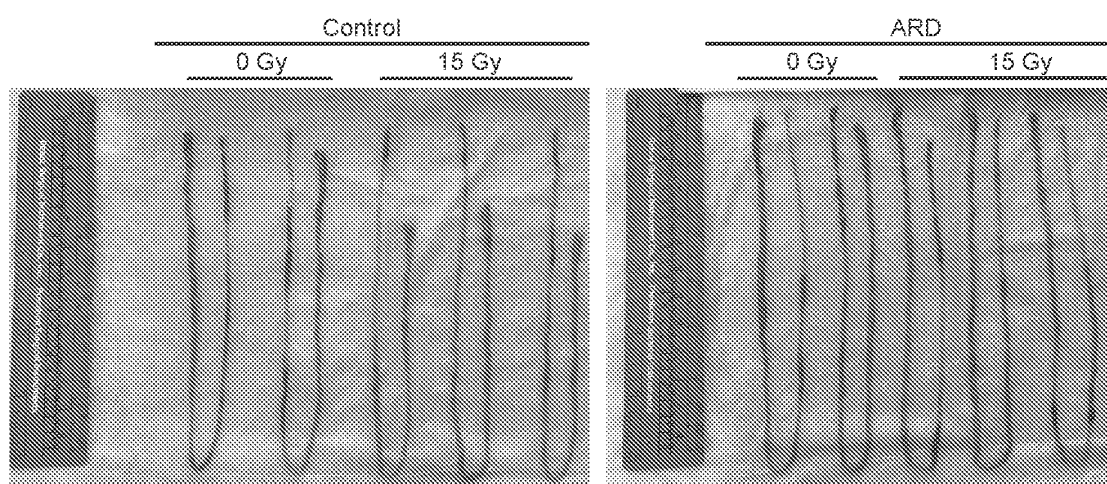


FIG. 9D

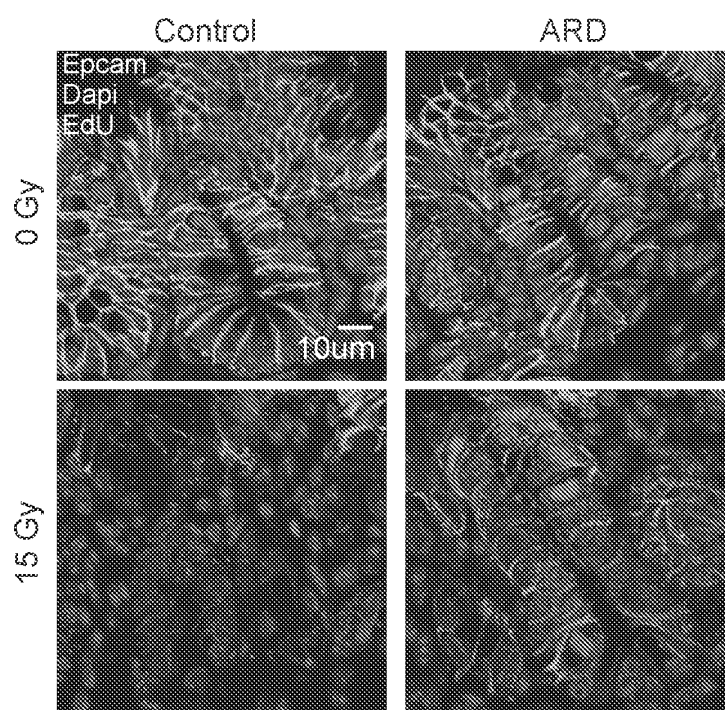


FIG. 9E

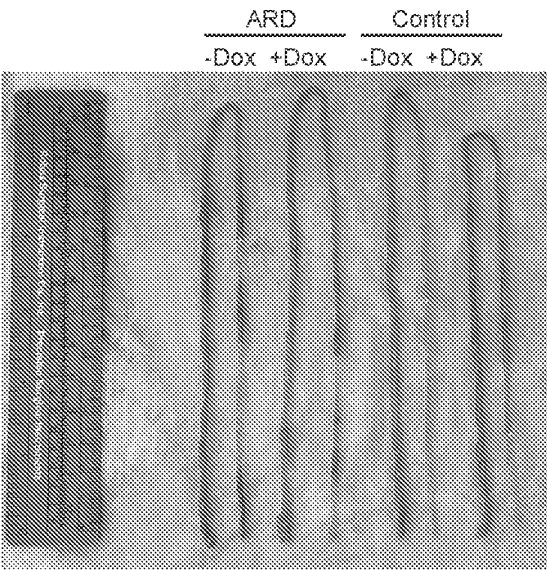


FIG. 9F

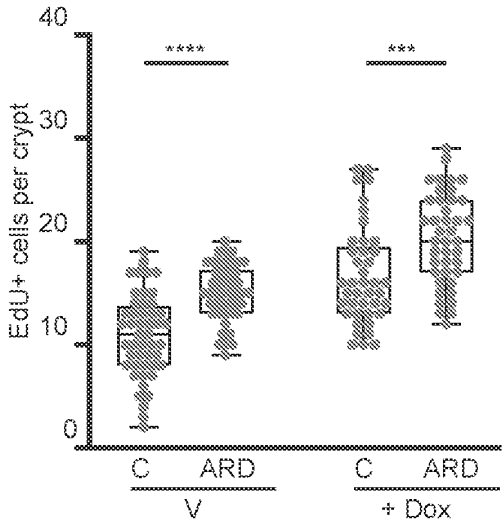


FIG. 9G

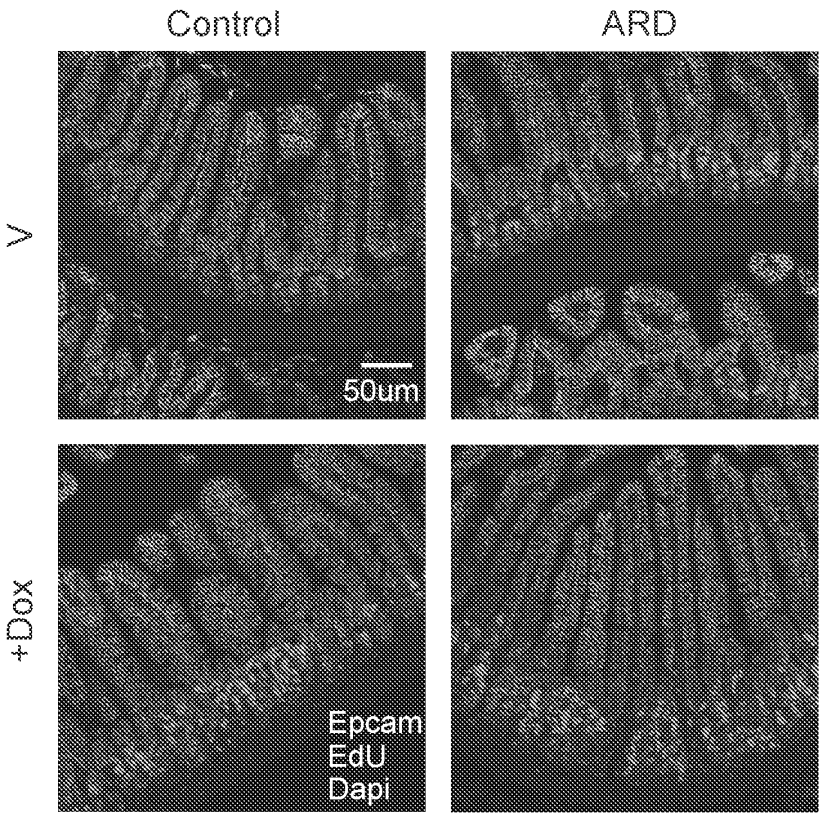


FIG. 9H

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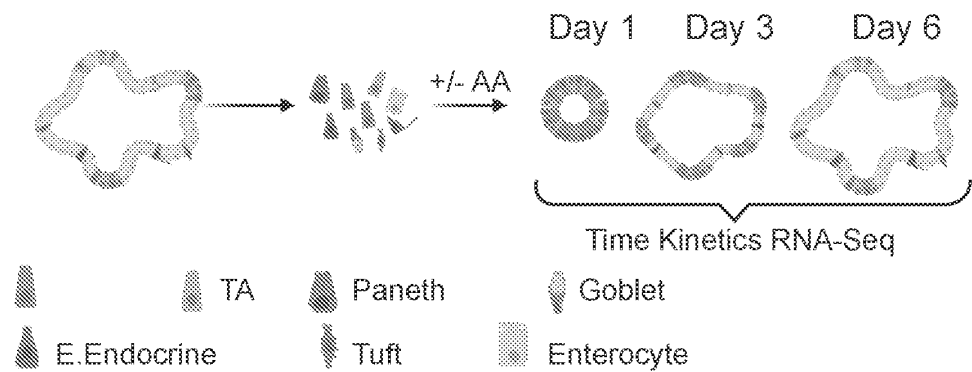


FIG. 10A

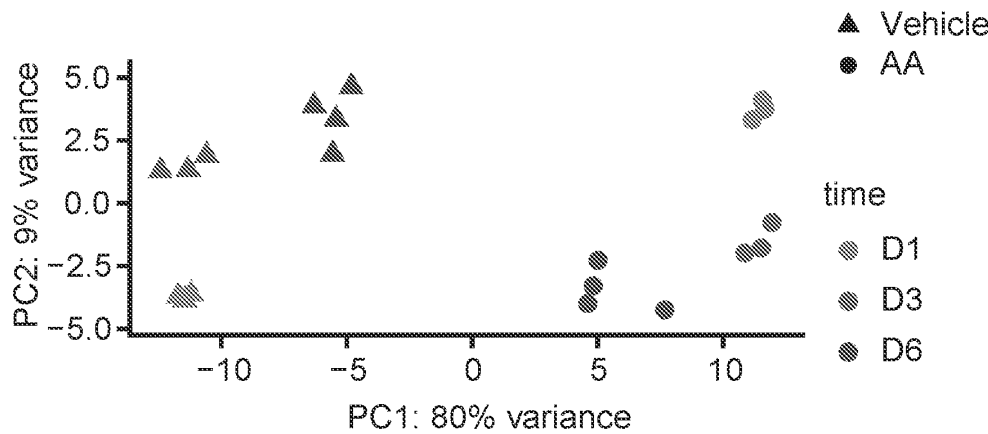


FIG. 10B

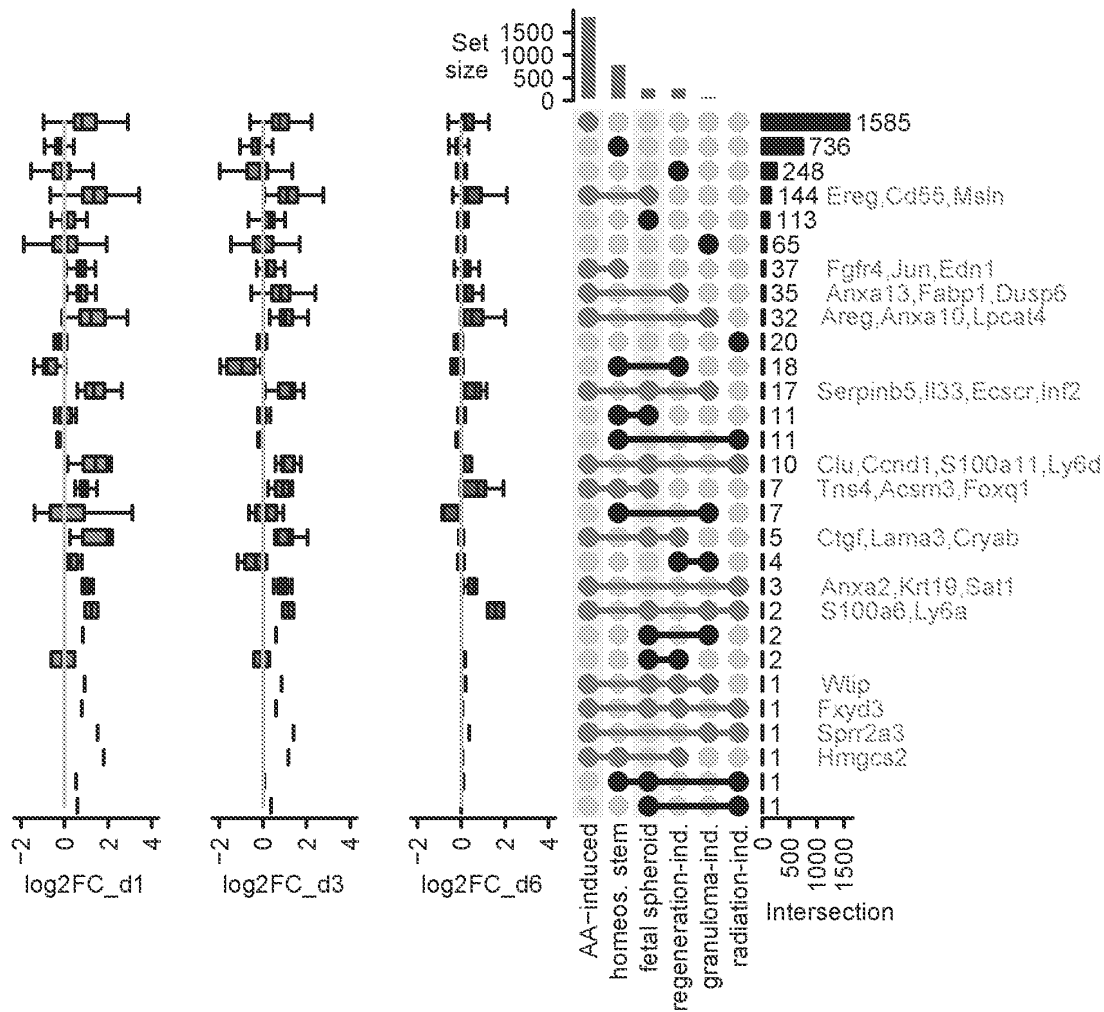


FIG. 10C

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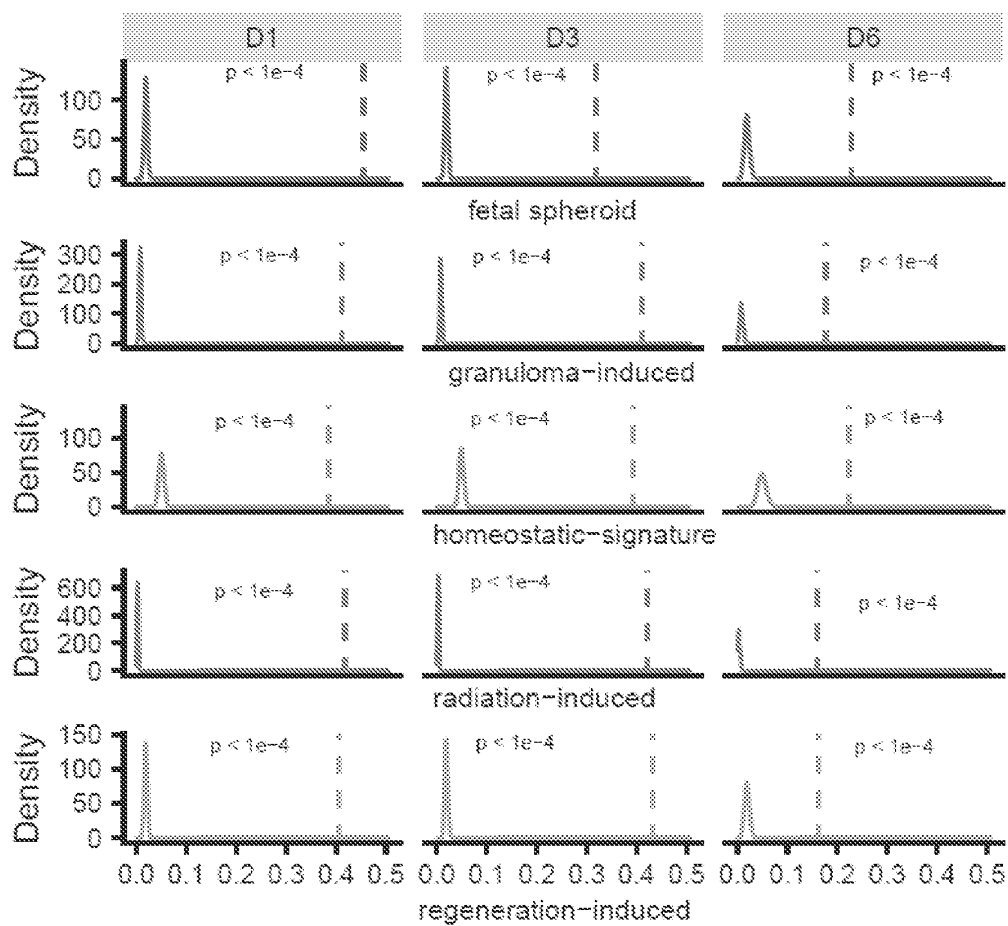


FIG. 10D

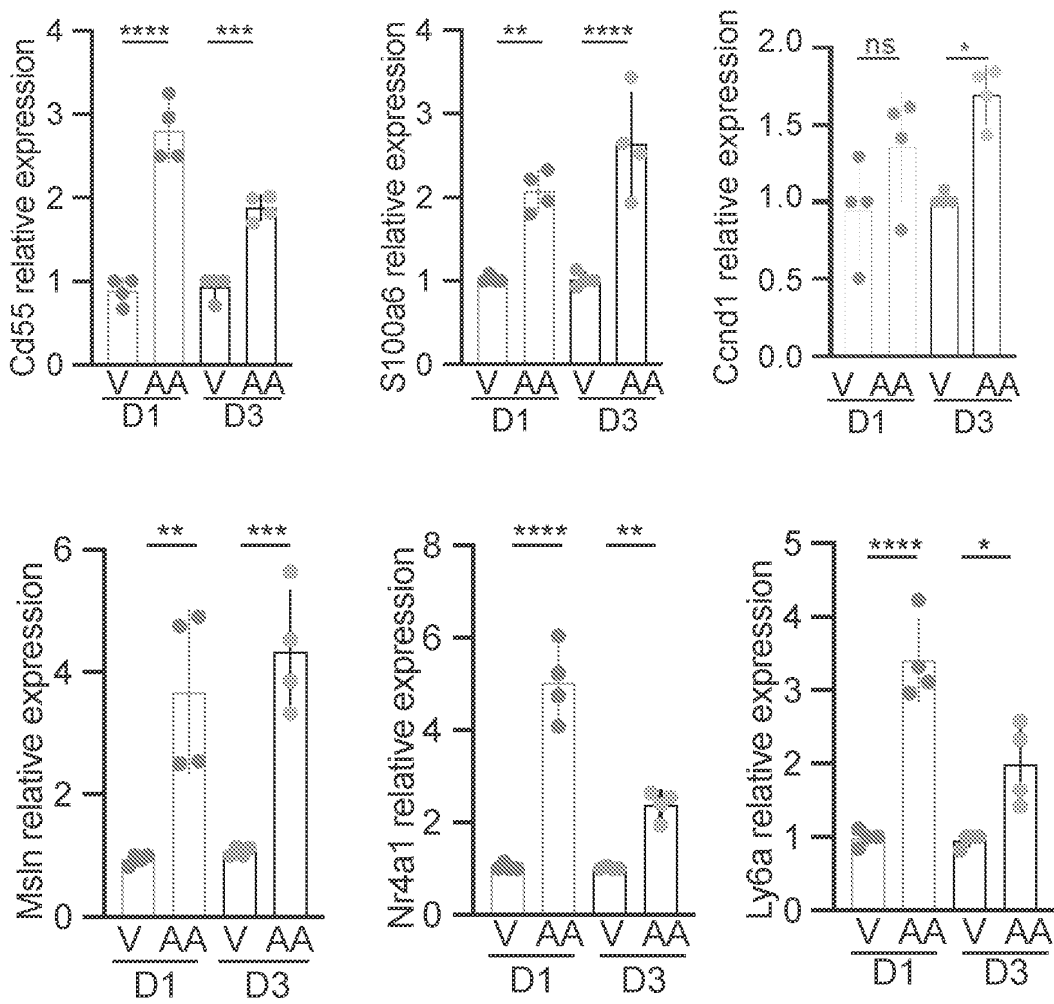


FIG. 10E

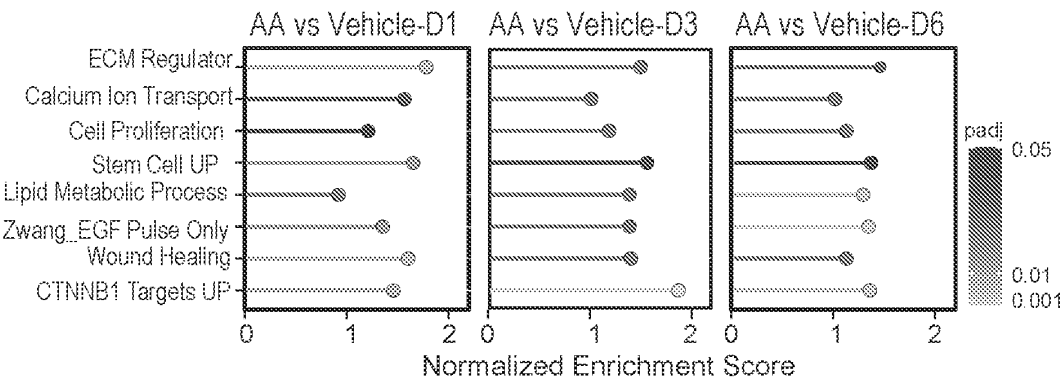


FIG. 10F

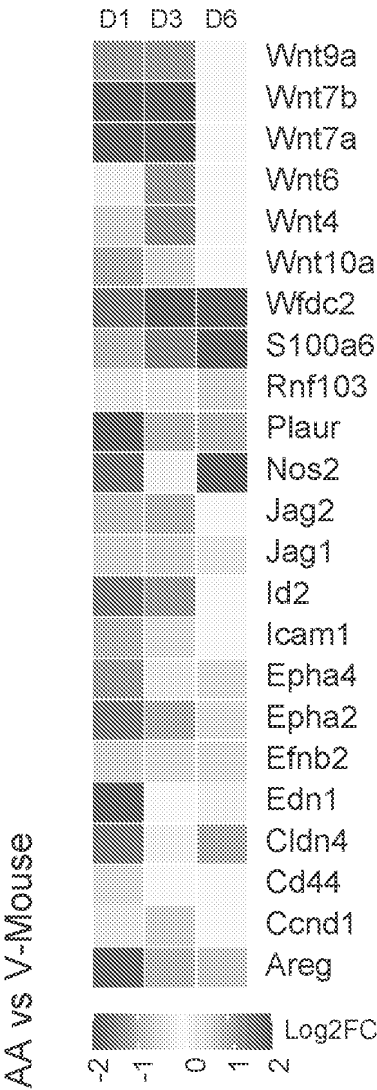


FIG. 10G

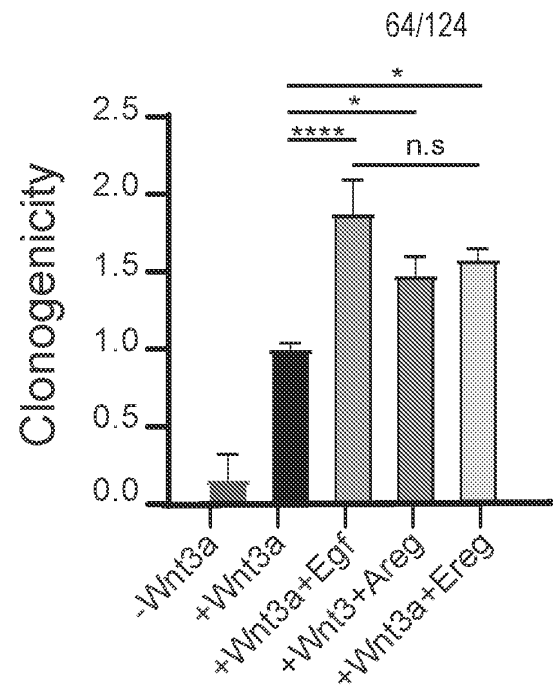


FIG. 10H

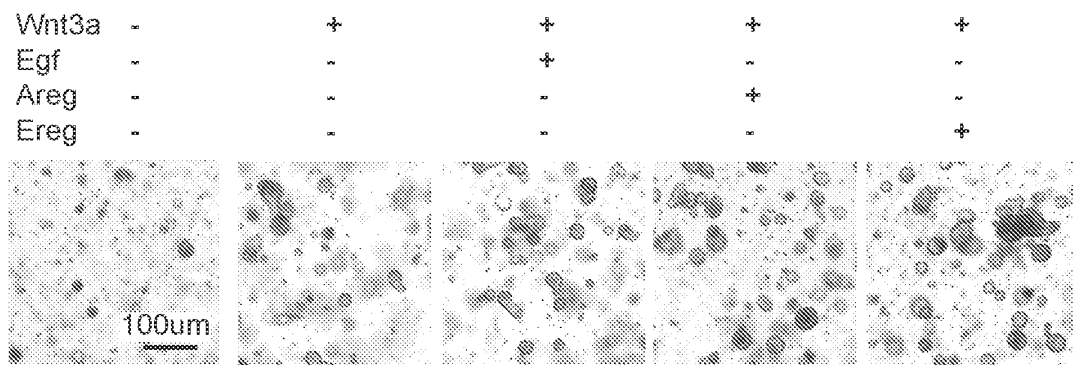


FIG. 10I

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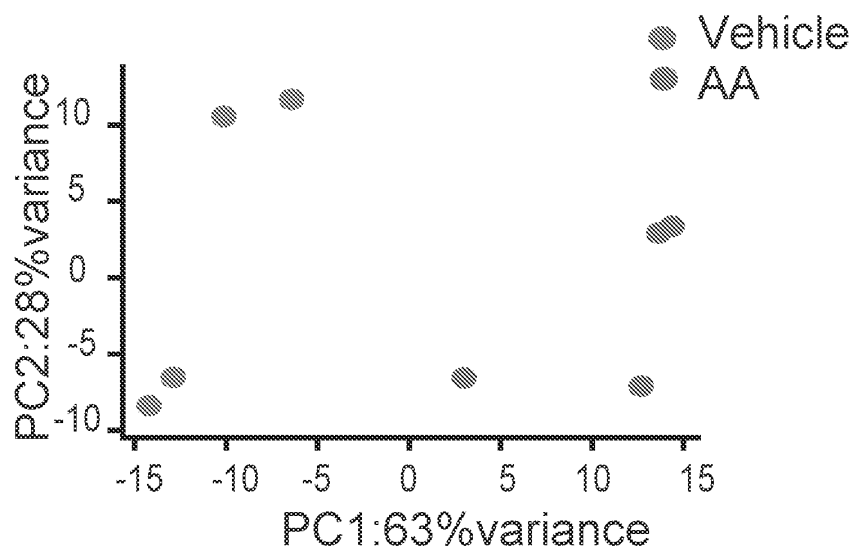


FIG. 10J

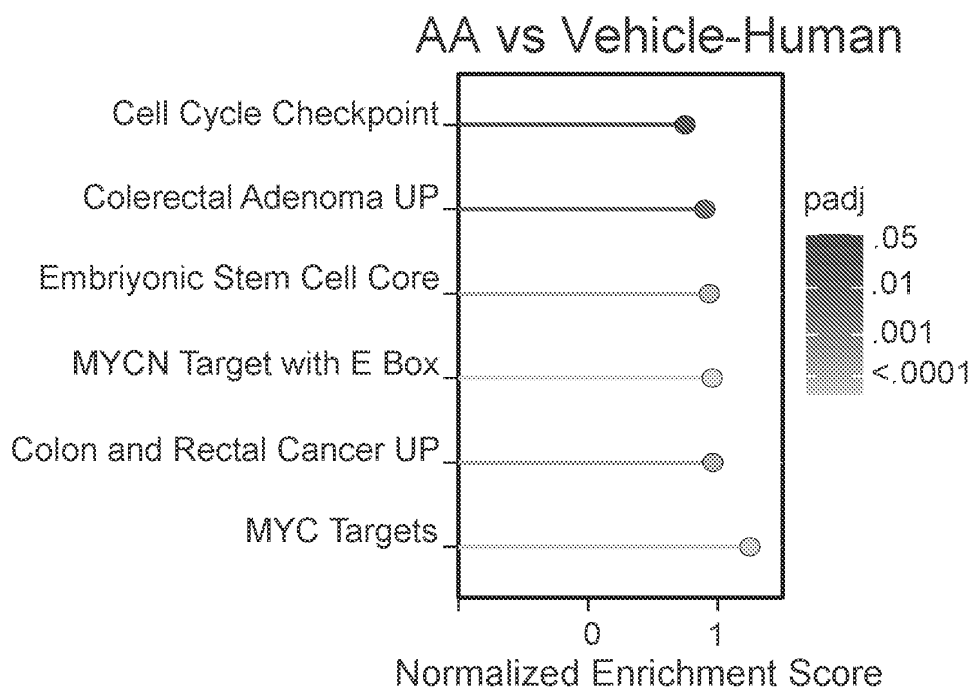


FIG. 10K

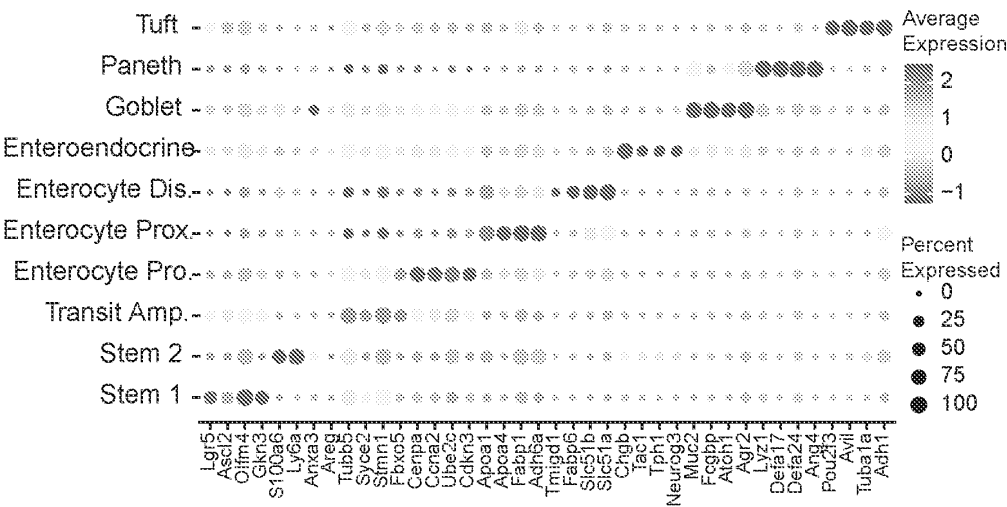


FIG. 11A

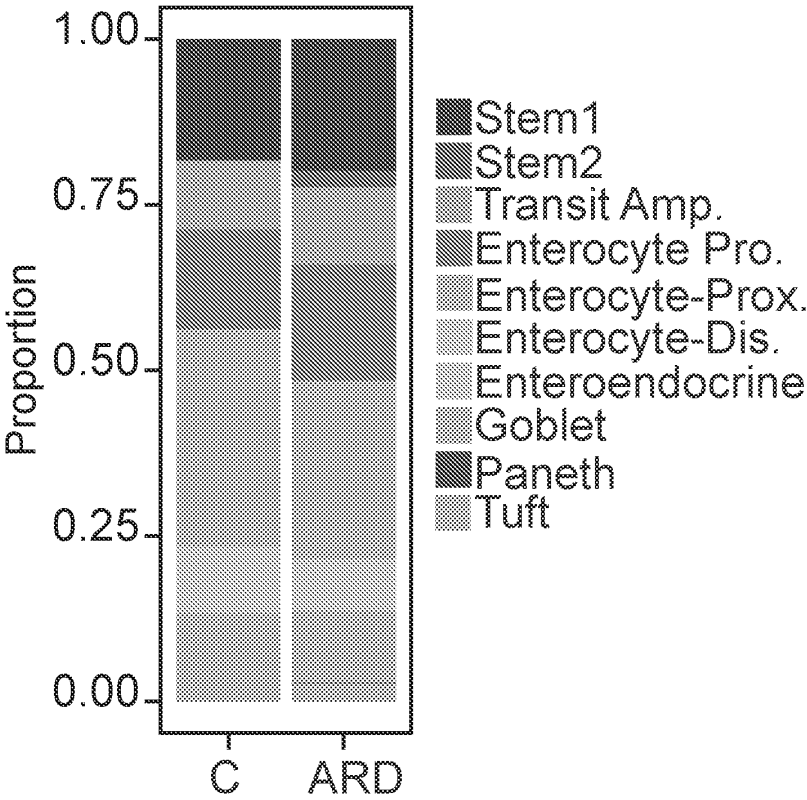


FIG. 11B

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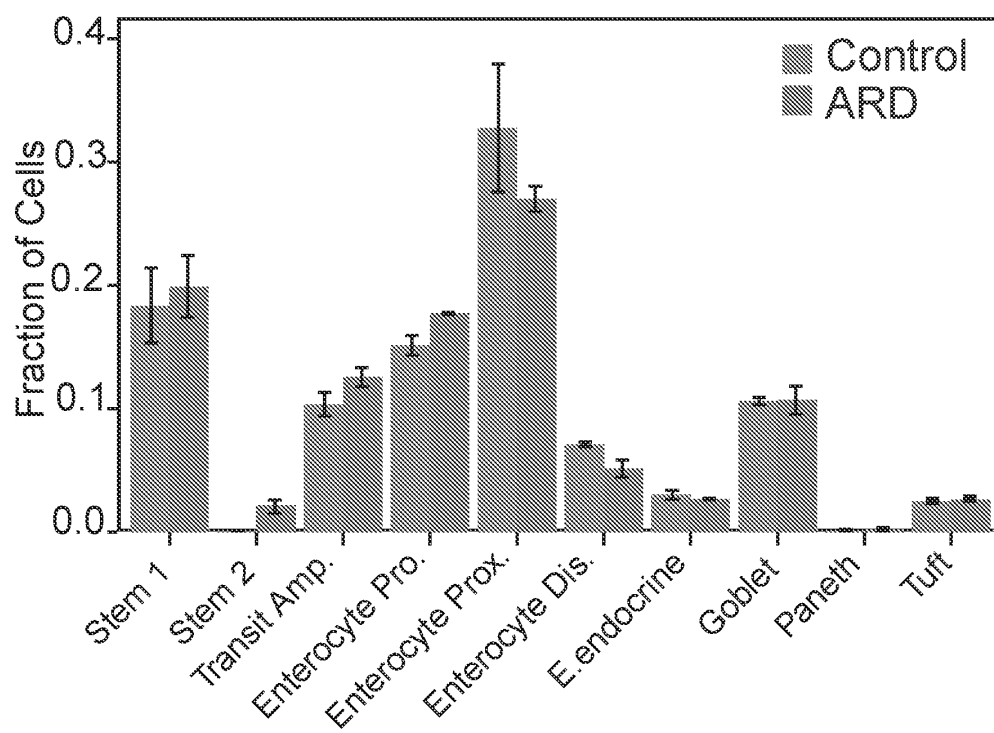


FIG. 11C

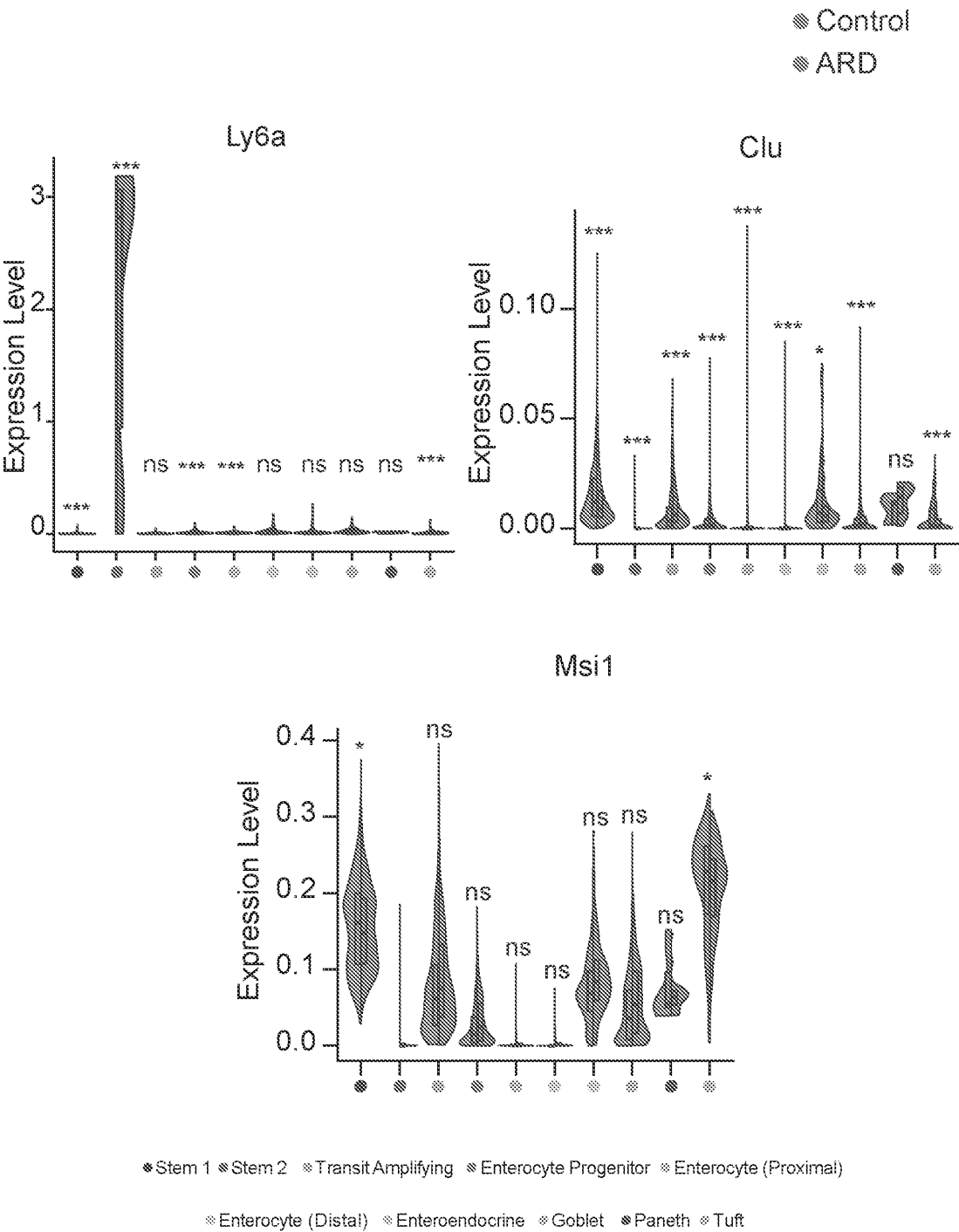


FIG. 11D

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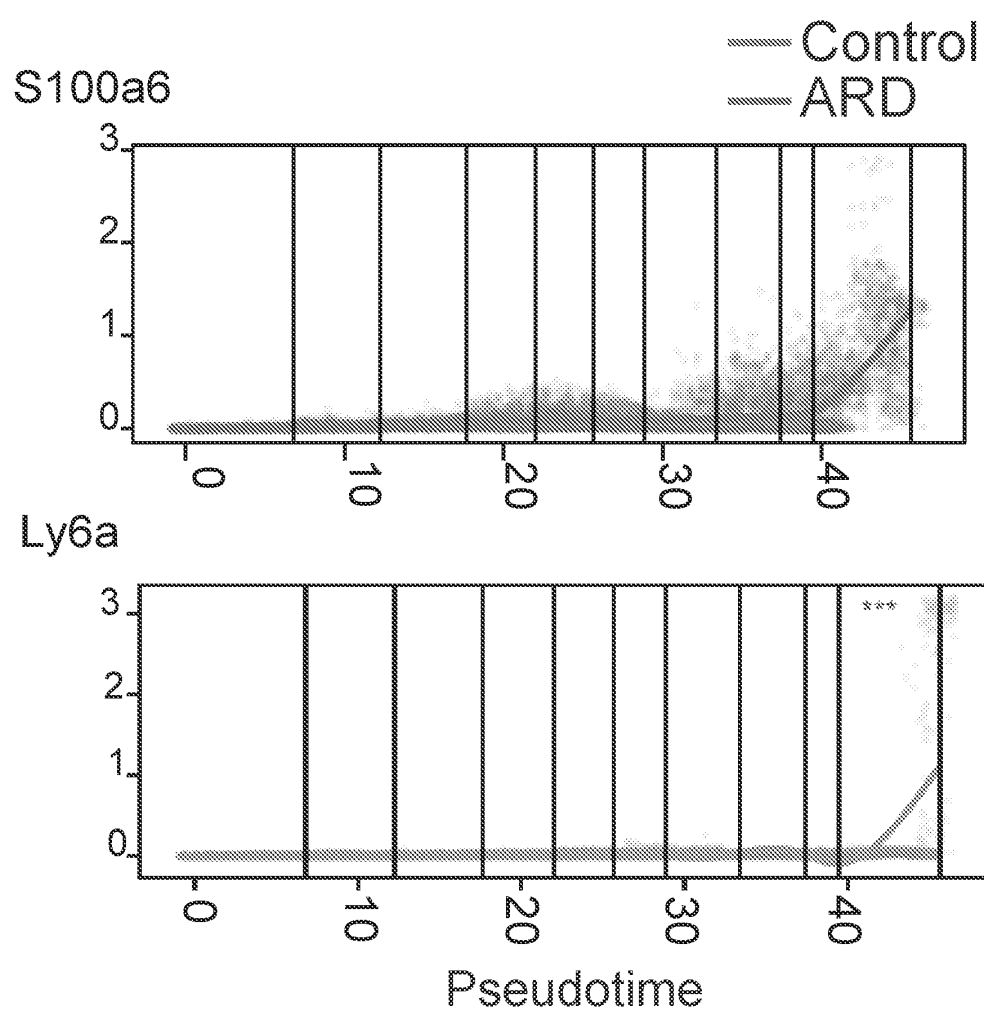


FIG. 11E

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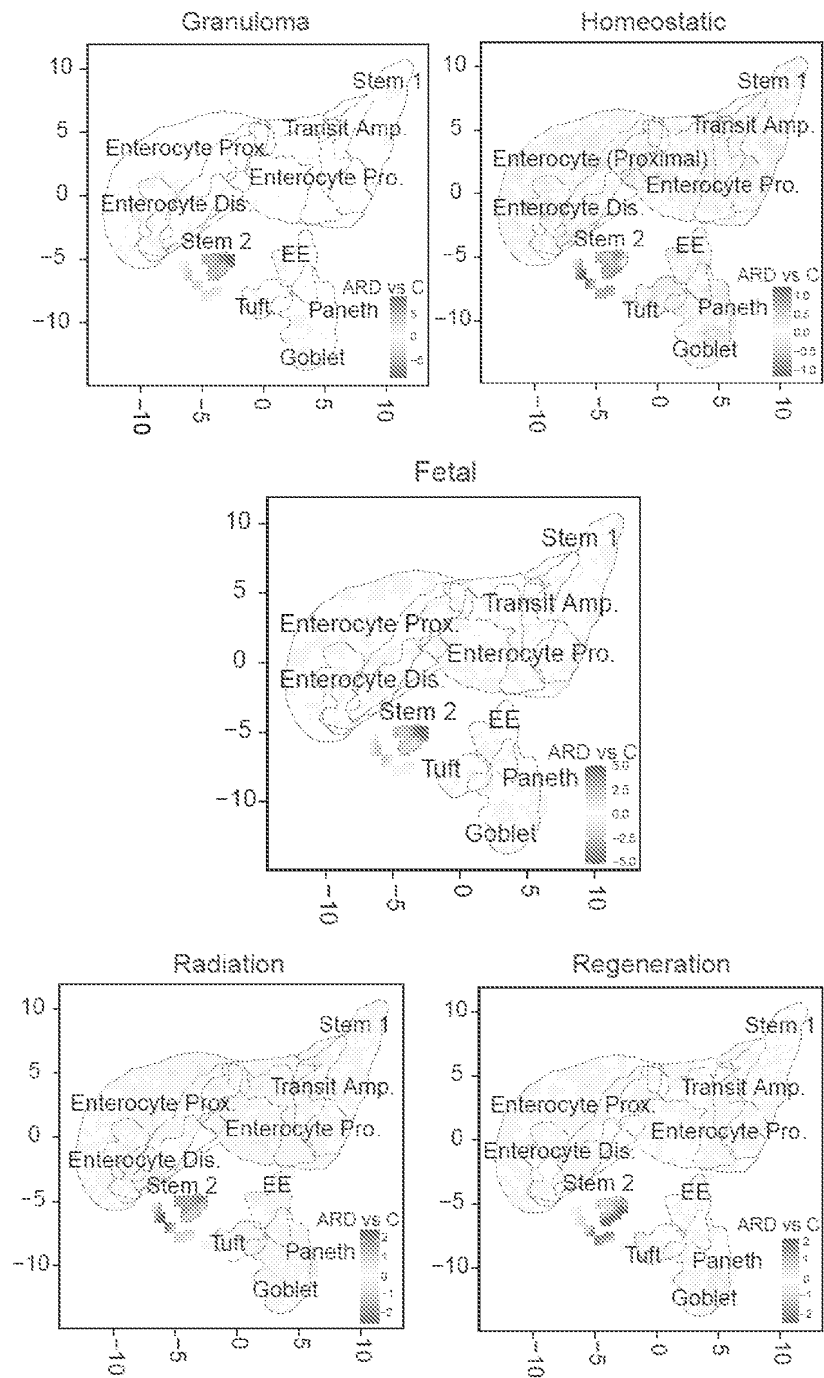


FIG. 11F

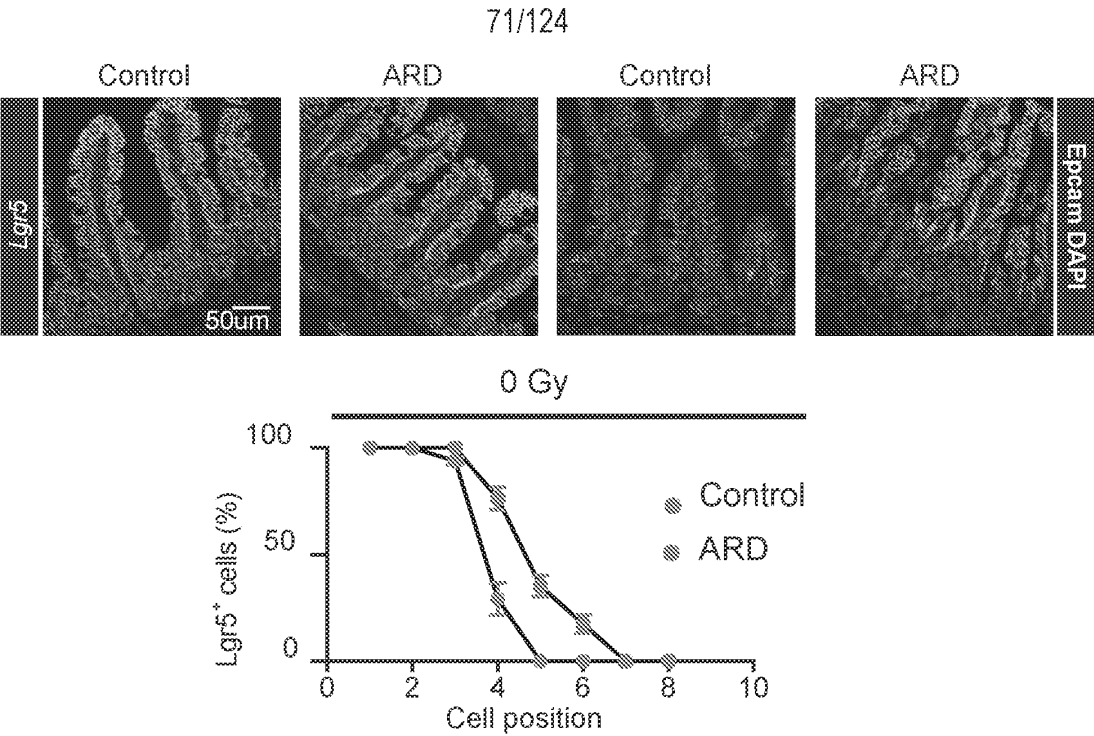


FIG. 11G

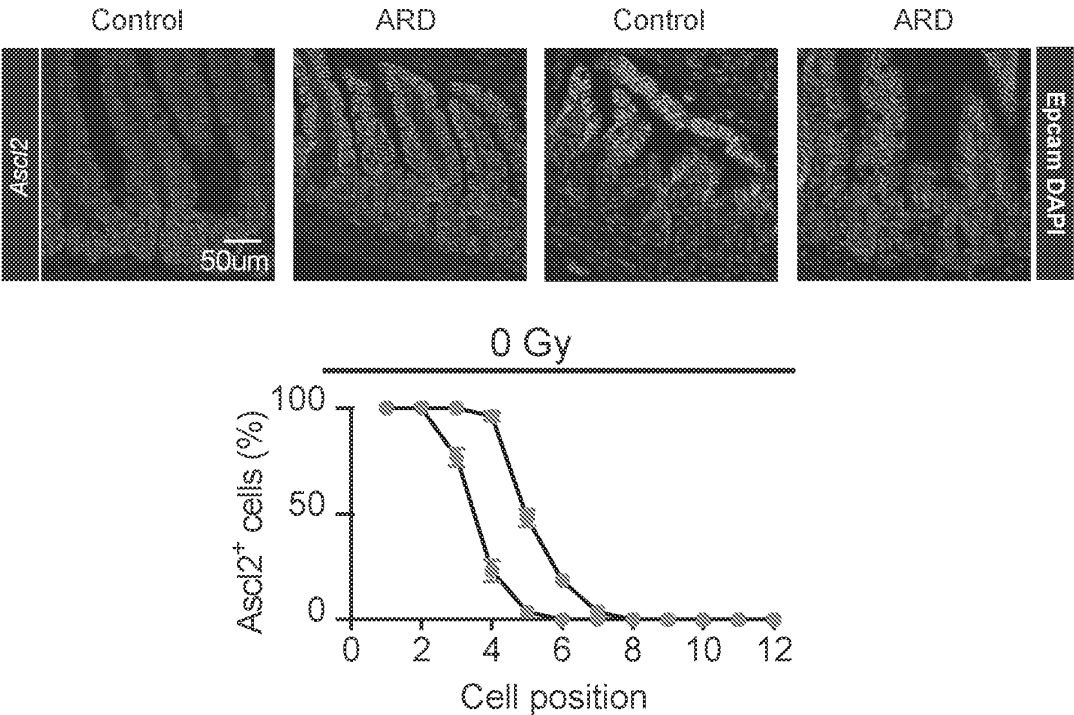


FIG. 11H

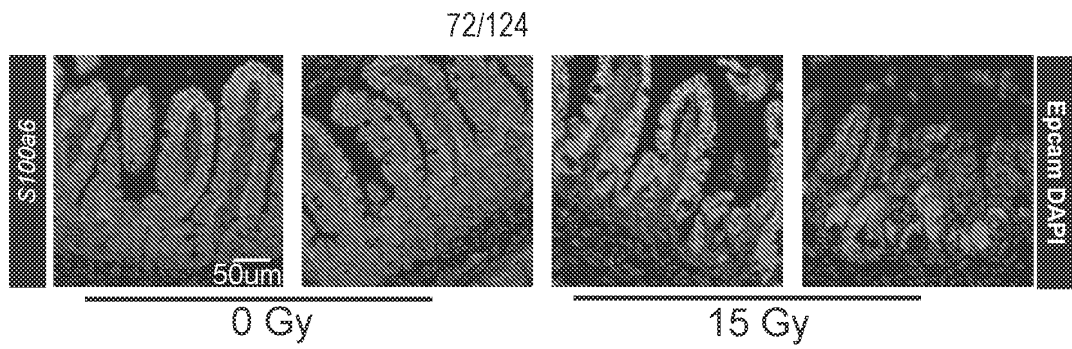
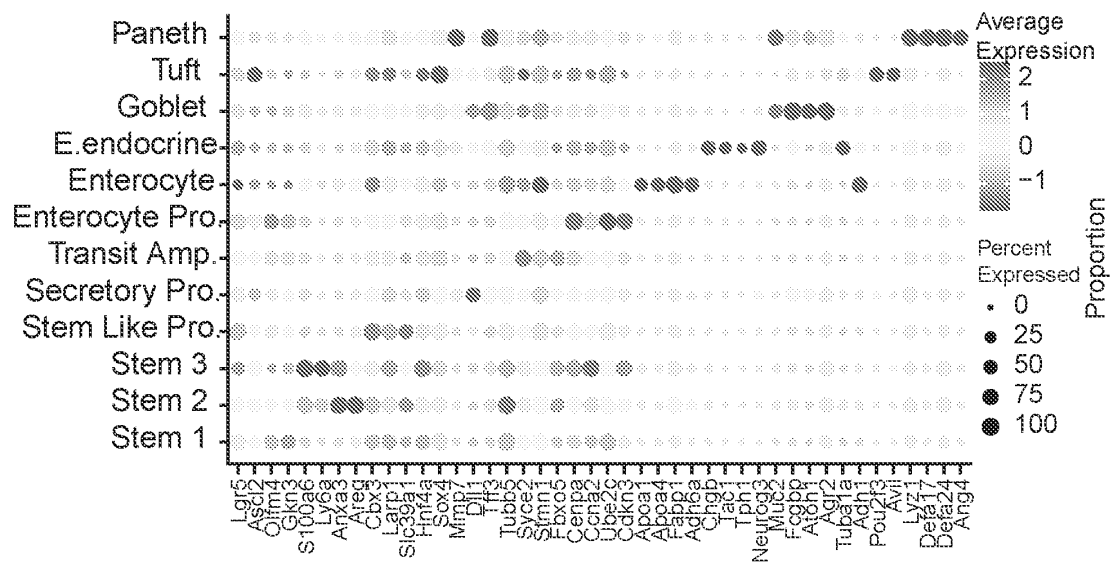


FIG. 111



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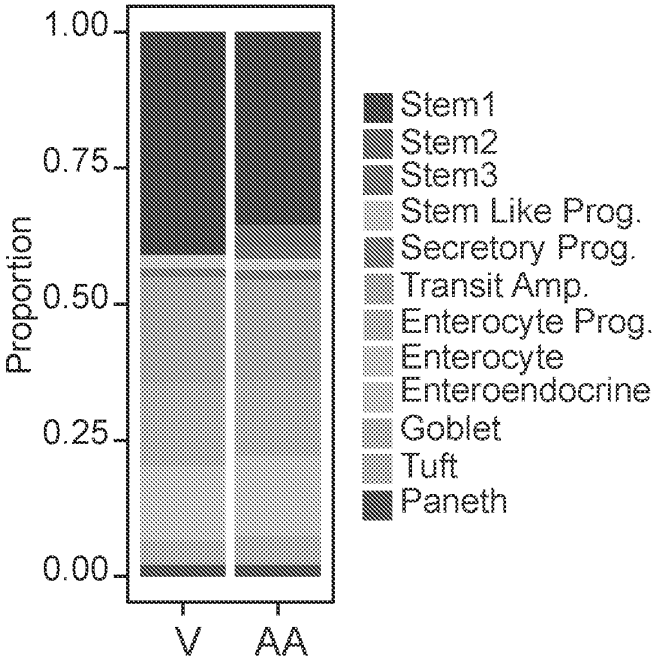


FIG. 12B

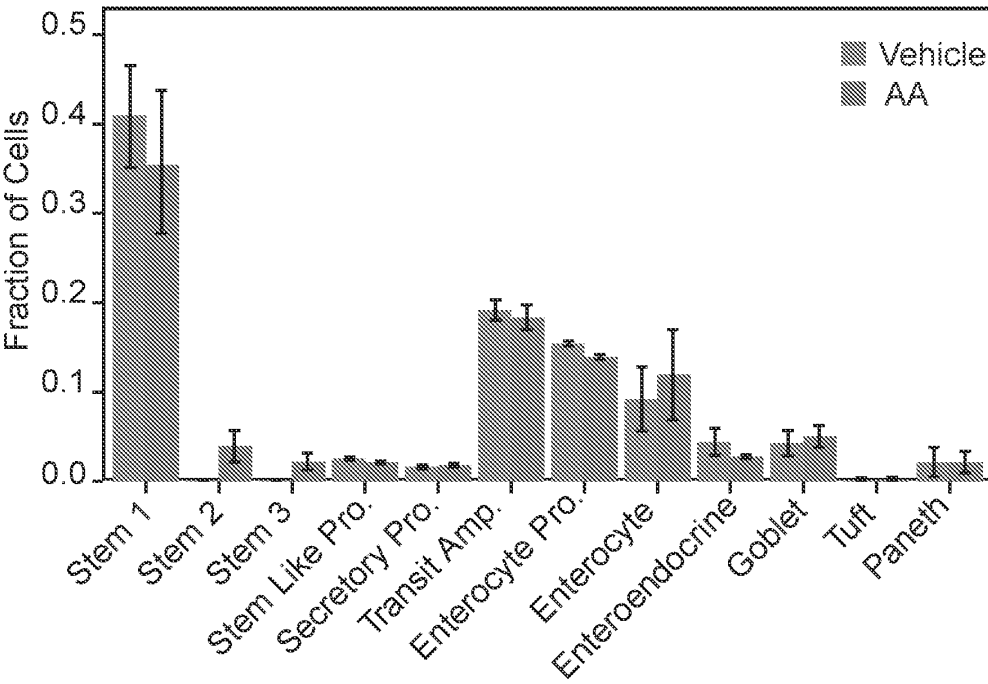


FIG. 12C

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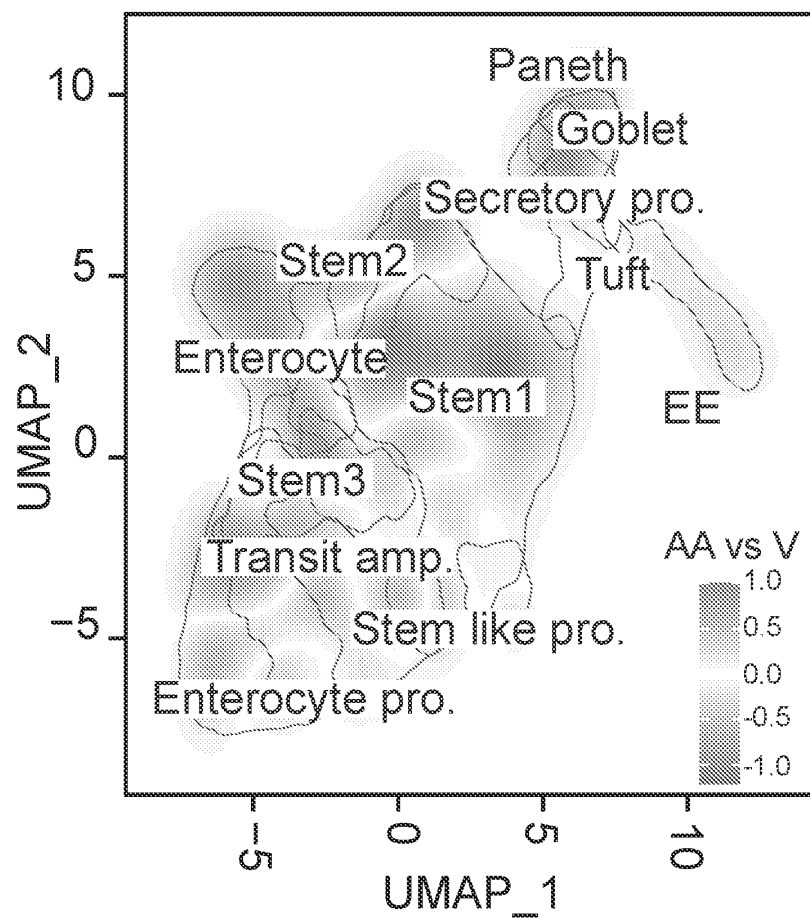


FIG. 12D

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● Stem 1 ● Stem 2 ● Stem 3 ● Stem Like Progenitor ● Secretory Progenitor ● Transit Amplifying
● Enterocyte Progenitor ● Enterocyte ● Enteroendocrine ● Goblet ● Tuft ● Paneth

● Vehicle
● AA

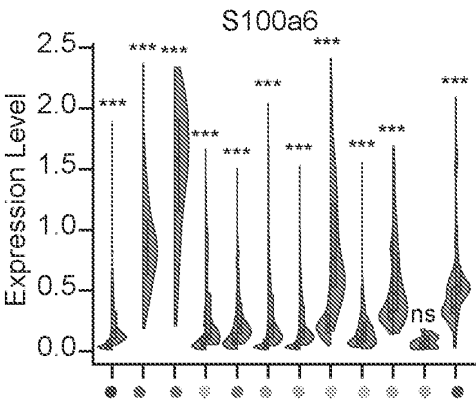


FIG. 12E

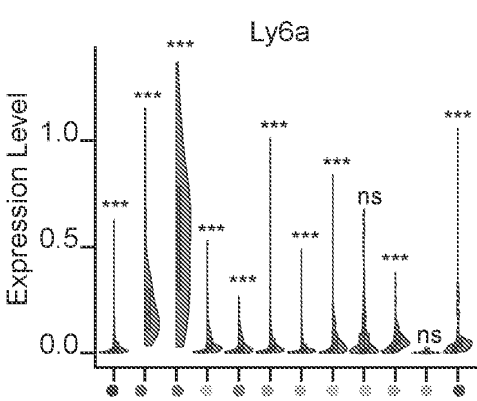


FIG. 12F

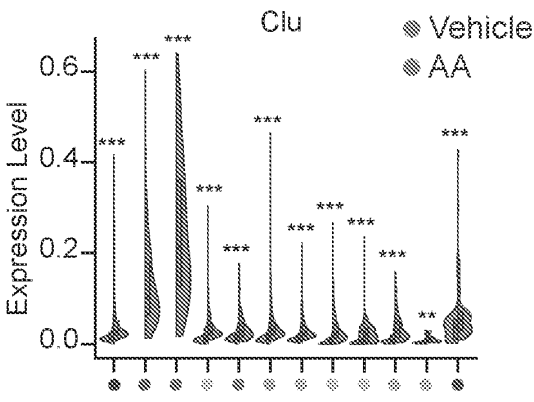


FIG. 12G

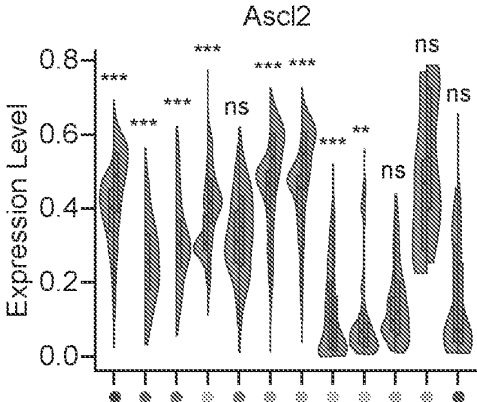


FIG. 12H

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- Stem 1 ● Stem 2 ● Stem 3 ● Stem Like Progenitor ● Secretory Progenitor ● Transit Amplifying
- Enterocyte Progenitor ● Enterocyte ● Enteroendocrine ● Goblet ● Tuft ● Paneth
- Vehicle
- AA

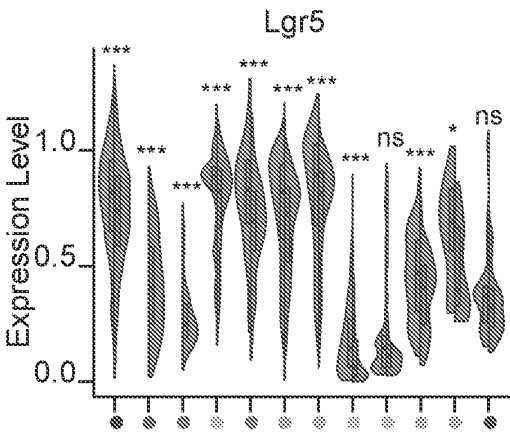


FIG. 12I

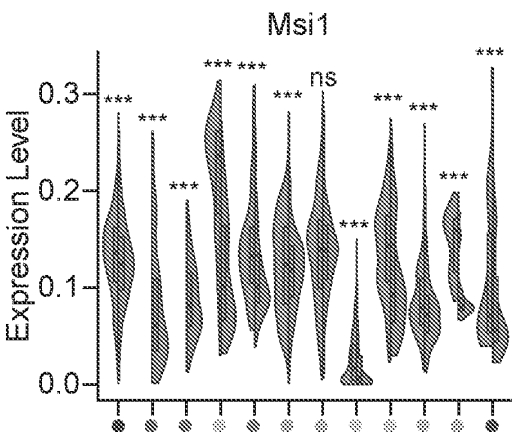


FIG. 12J

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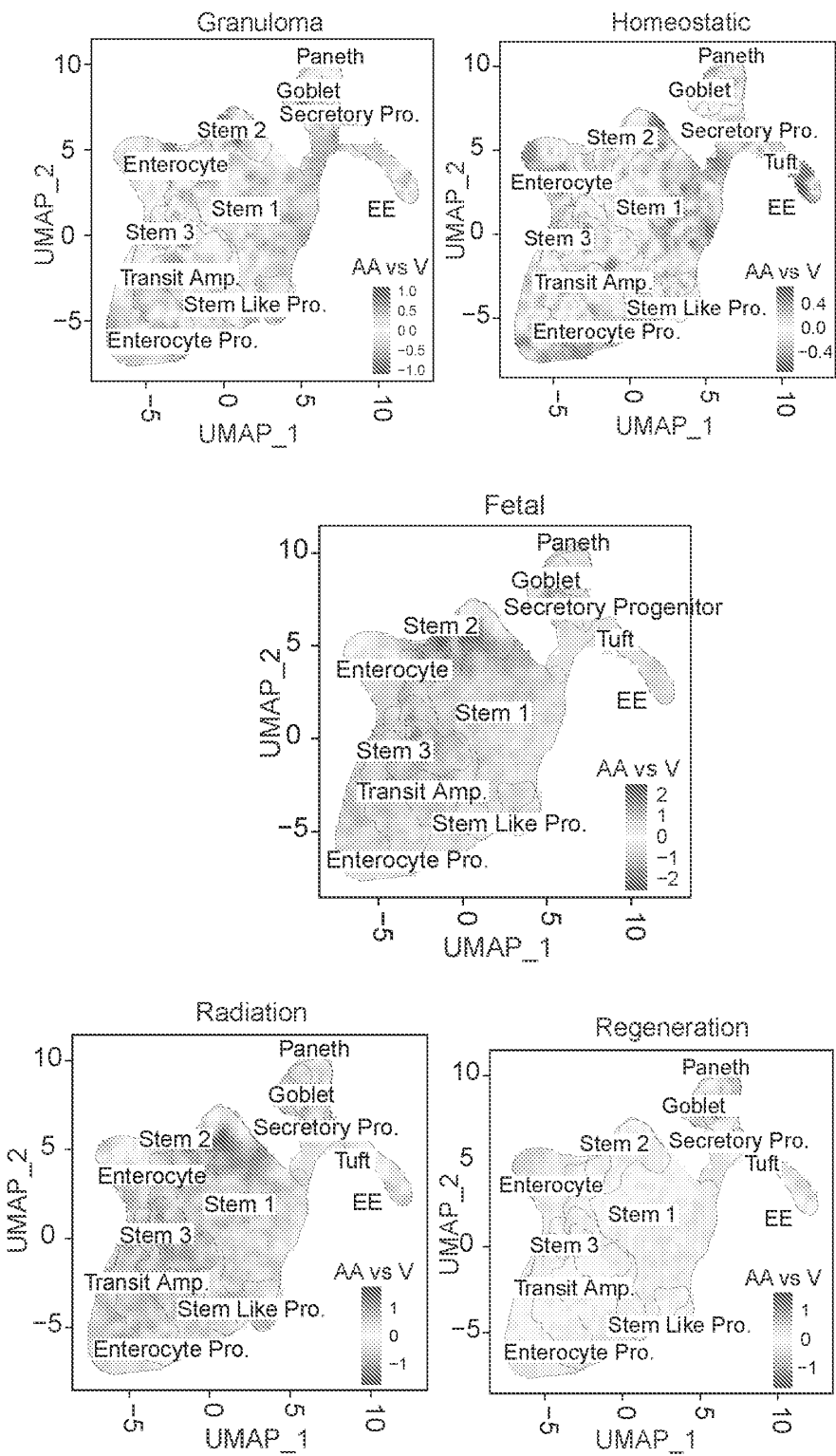


FIG. 12K

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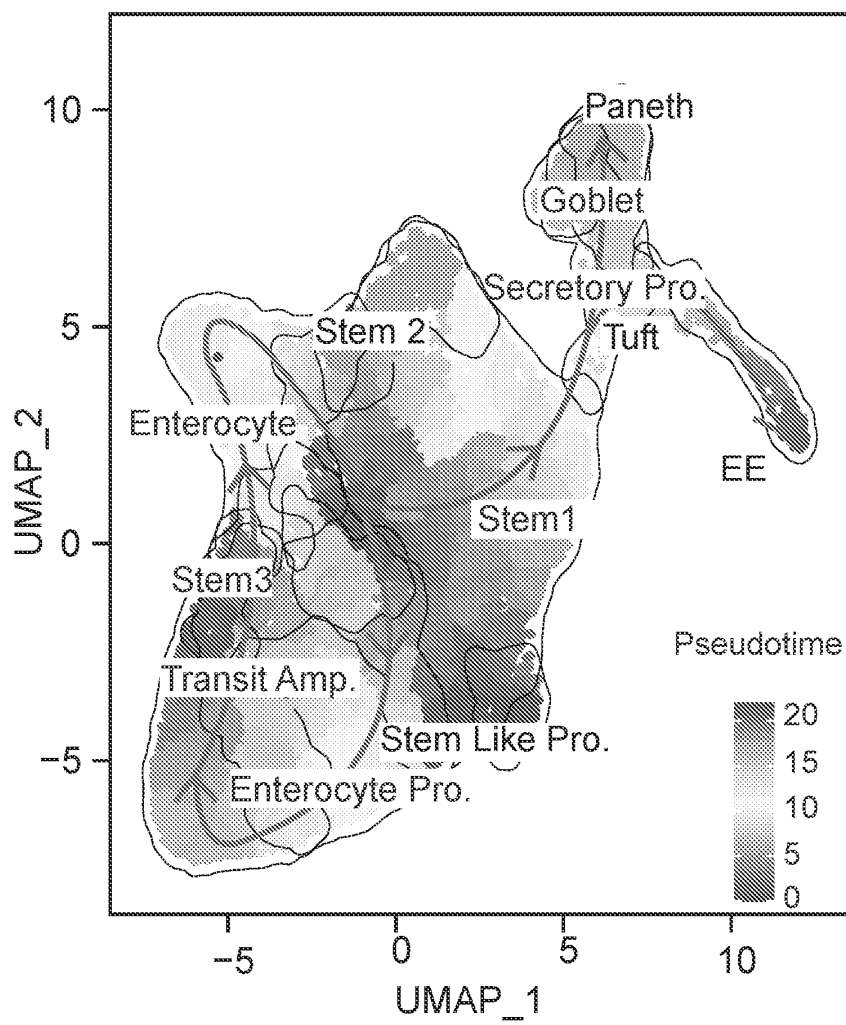


FIG. 12L

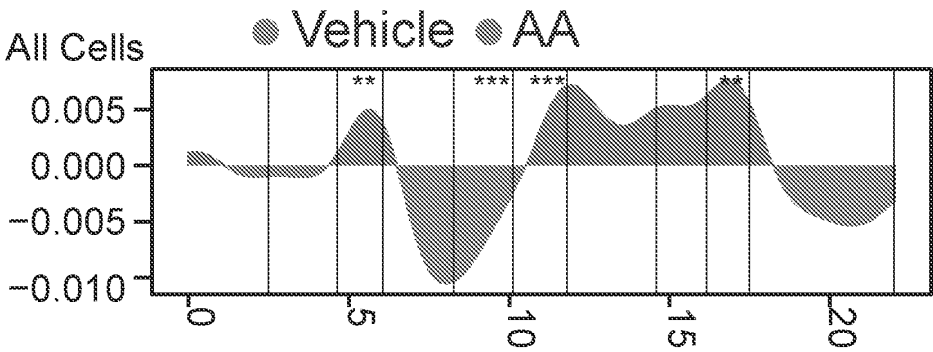


FIG. 12M

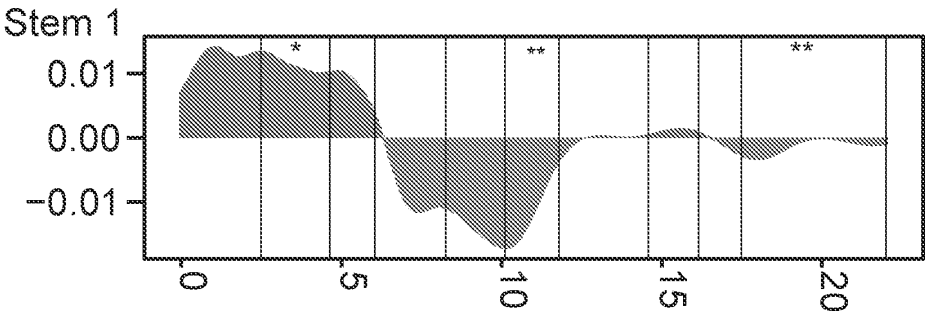


FIG. 12N

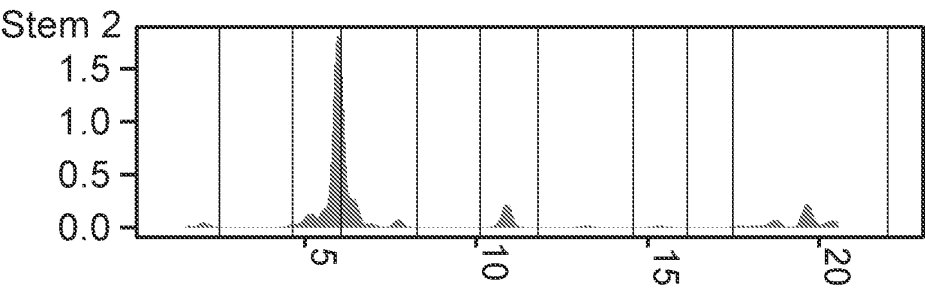


FIG. 12O

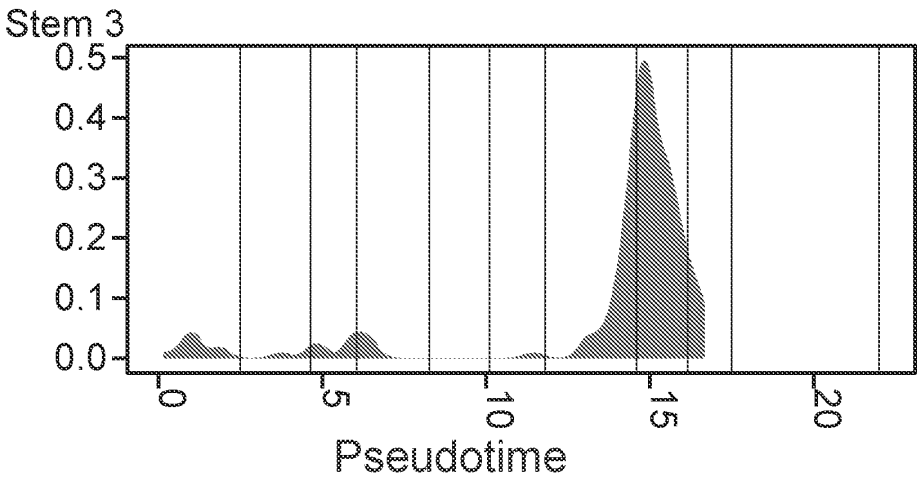


FIG. 12P

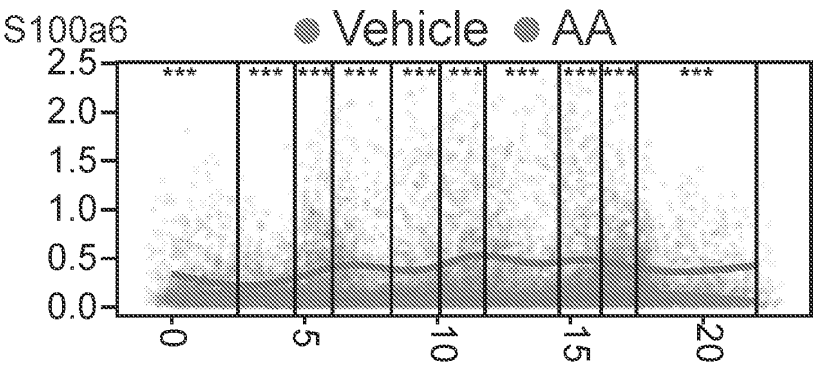


FIG. 12Q

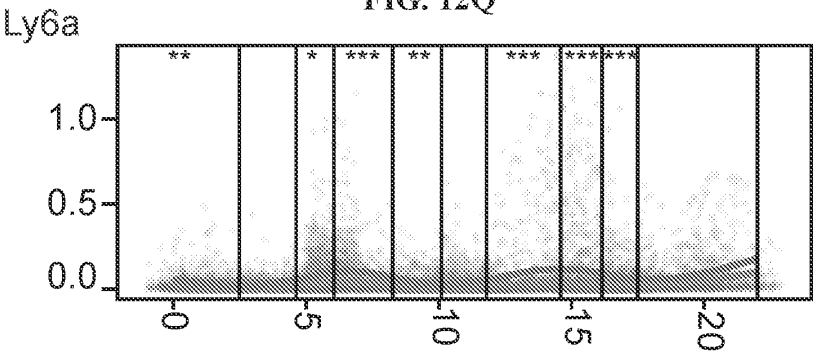


FIG. 12R

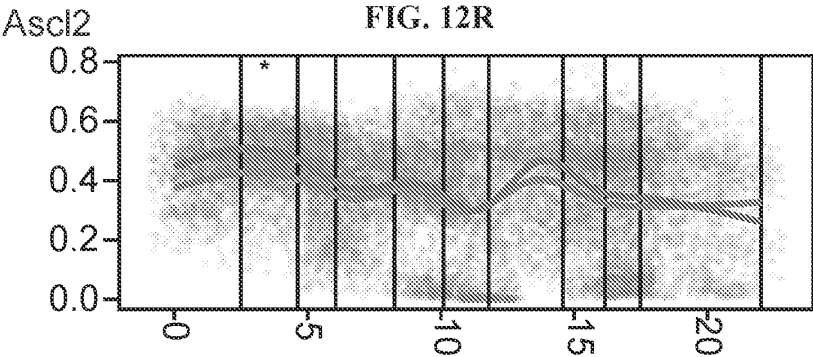
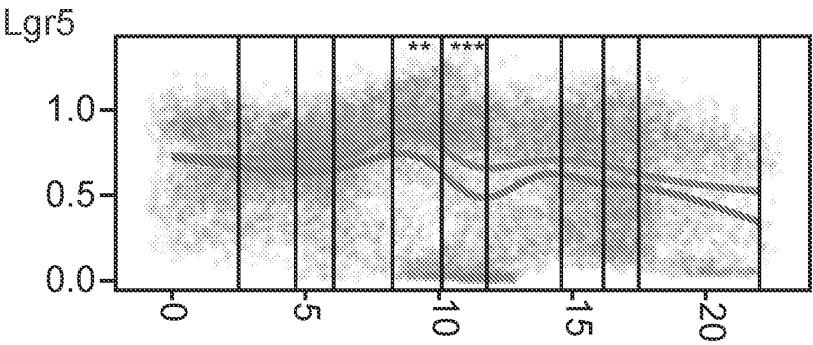


FIG. 12S



Pseudotime

FIG. 12T

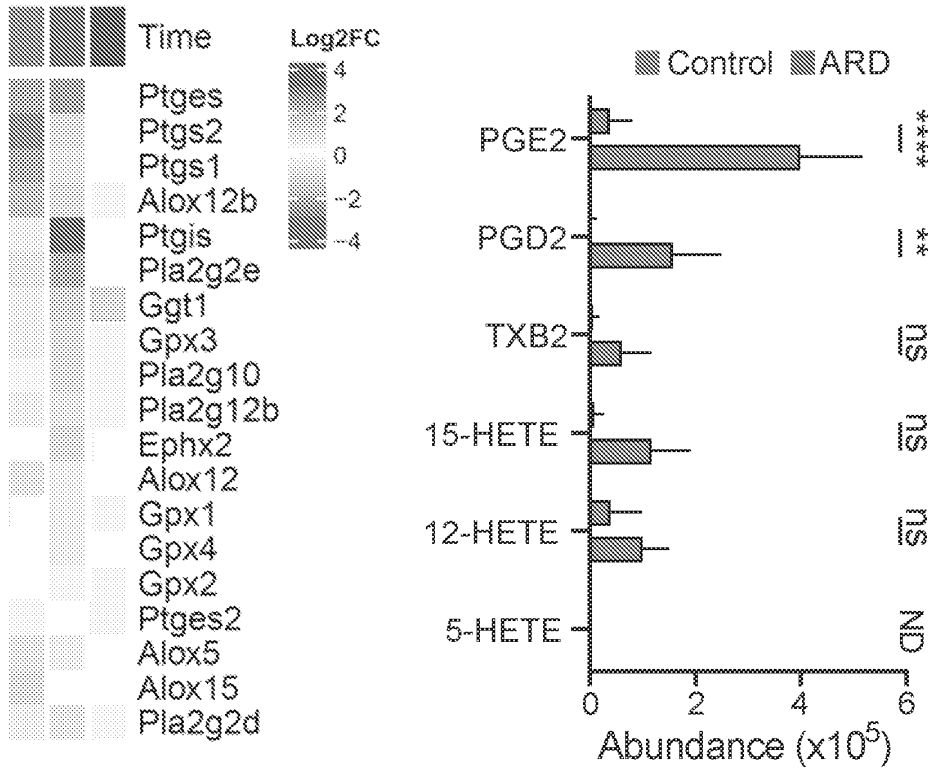


FIG. 13A

FIG. 13B

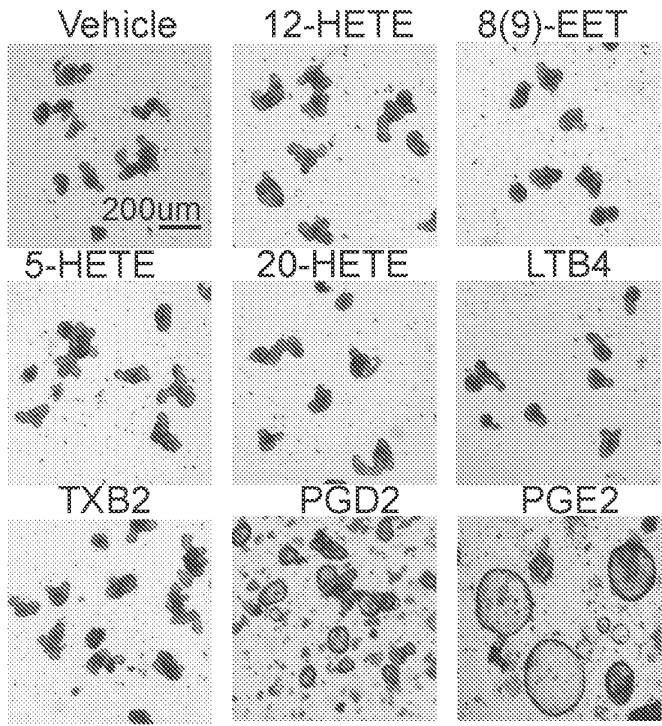


FIG. 13C

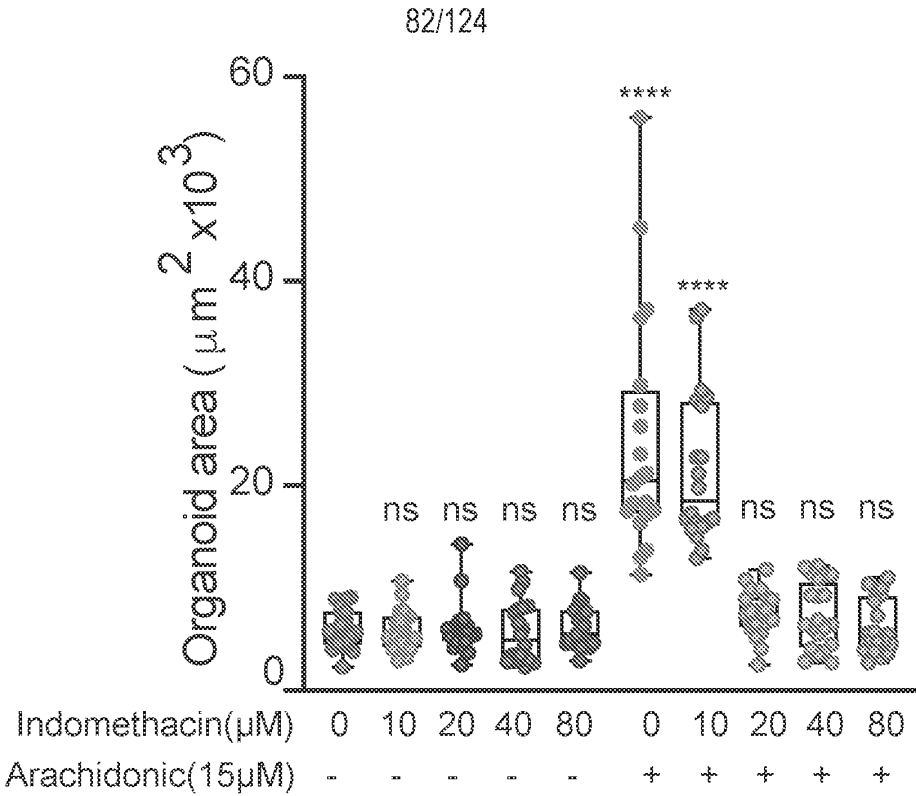


FIG. 13D

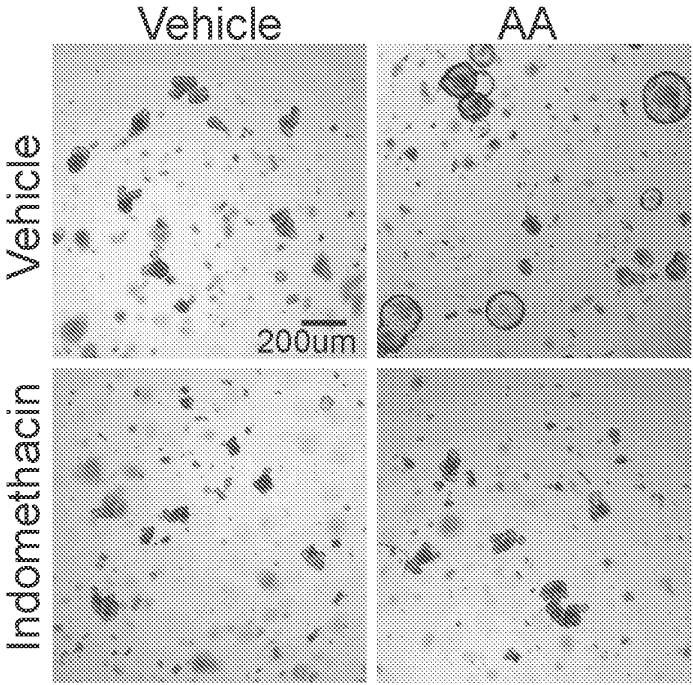


FIG. 13E

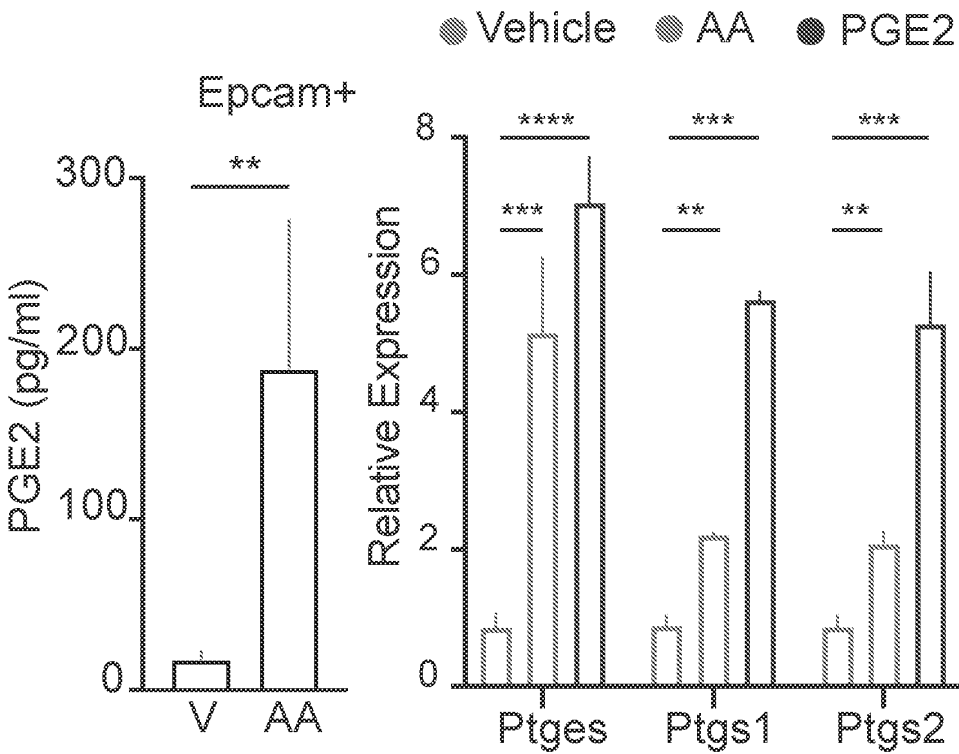


FIG. 13F

FIG. 13G

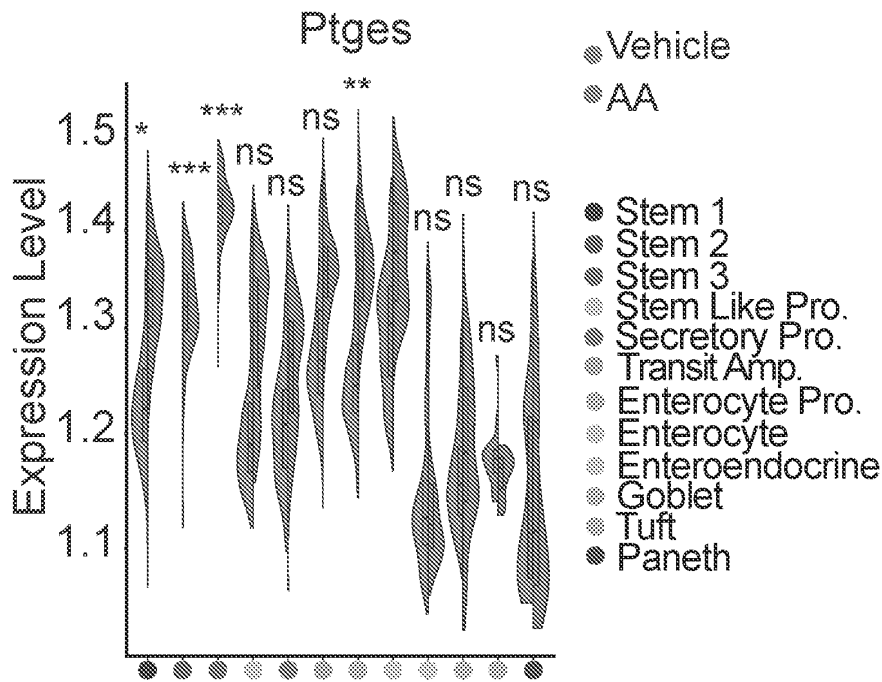


FIG. 13H

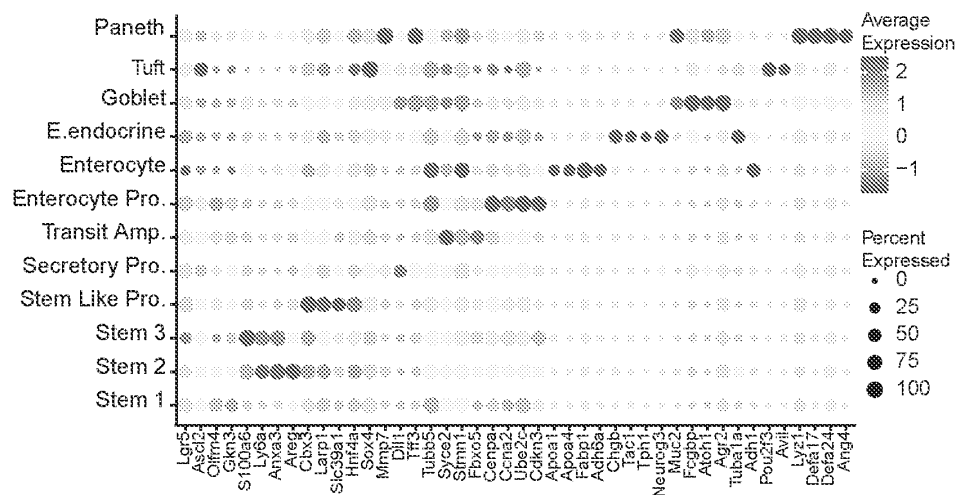


FIG. 13I

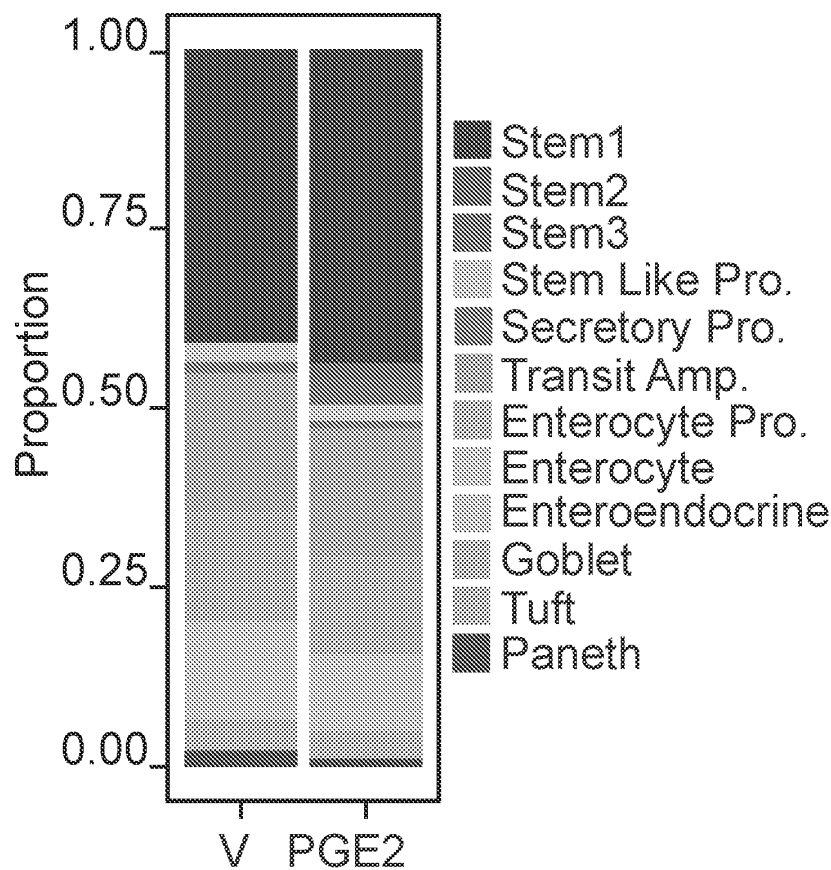


FIG. 13J

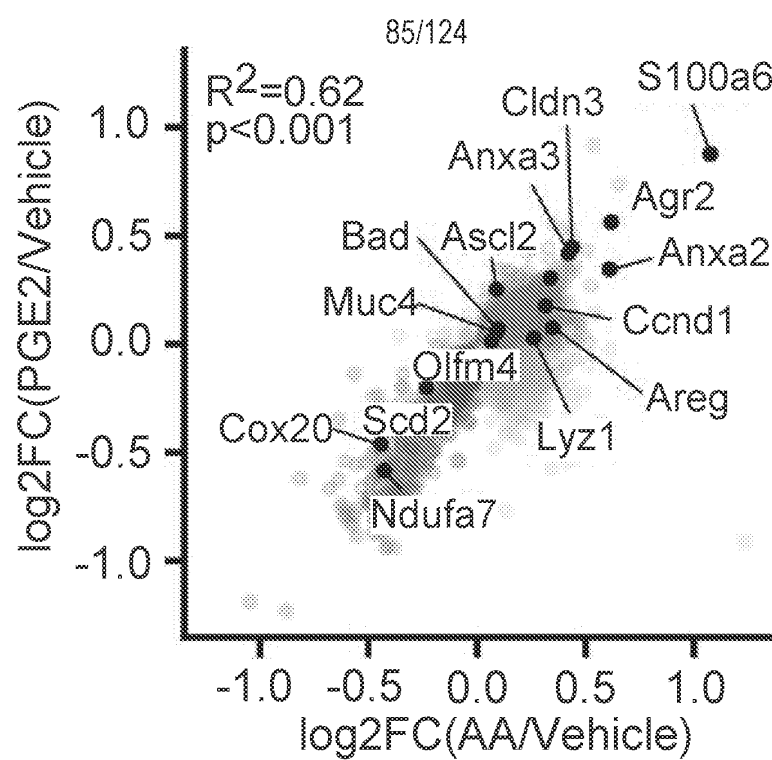


FIG. 13K

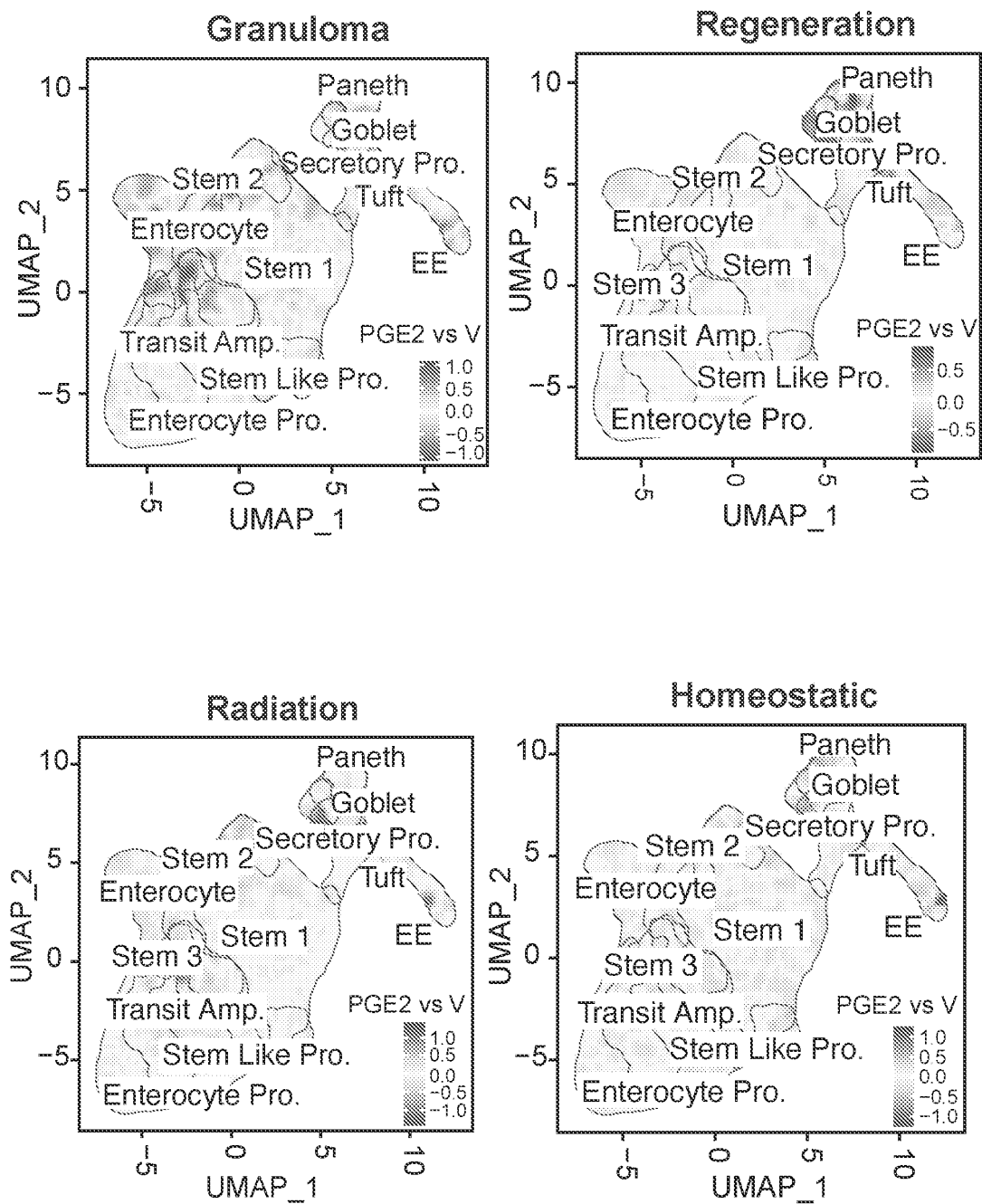


FIG. 13L

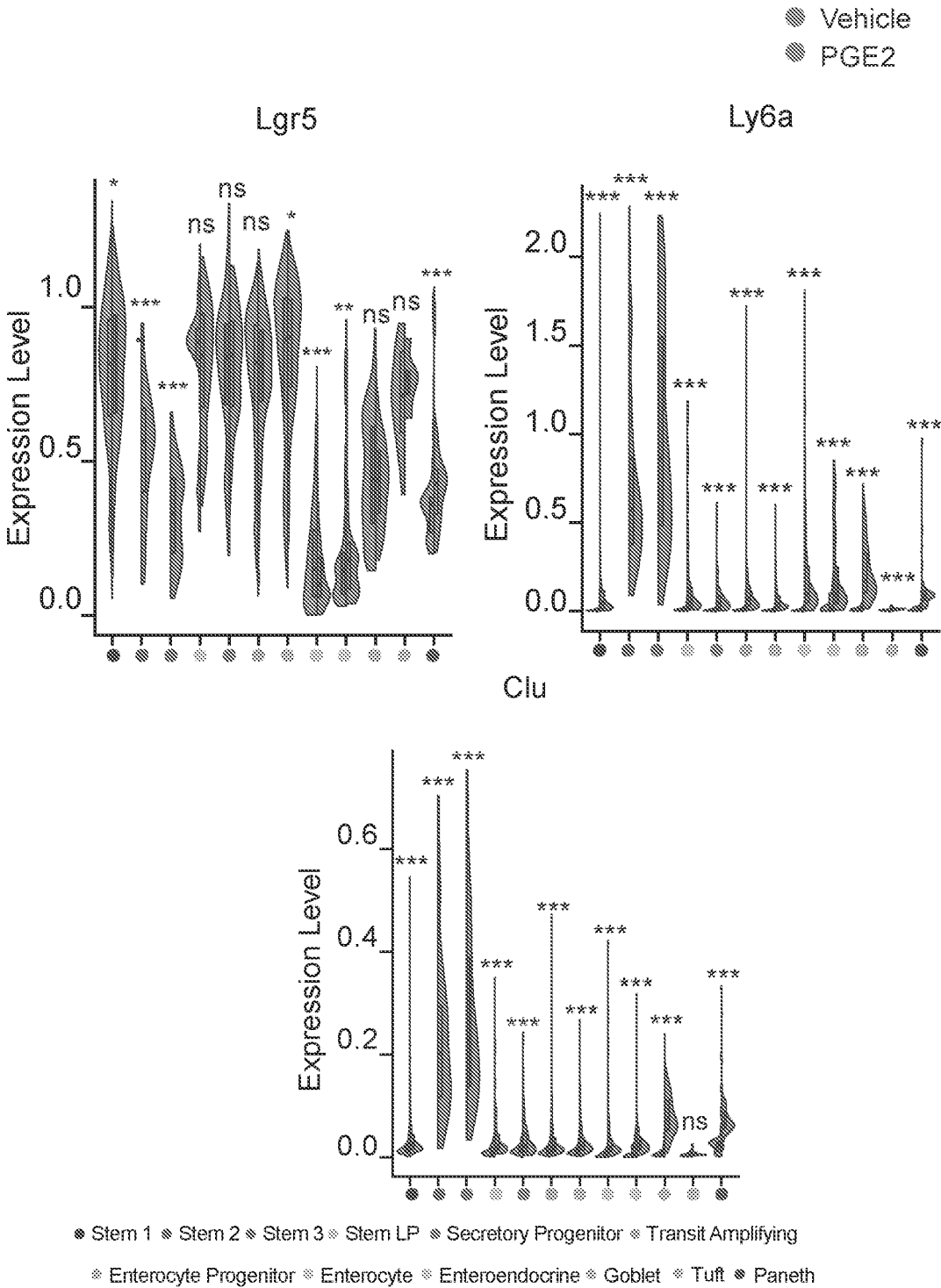


FIG. 13M

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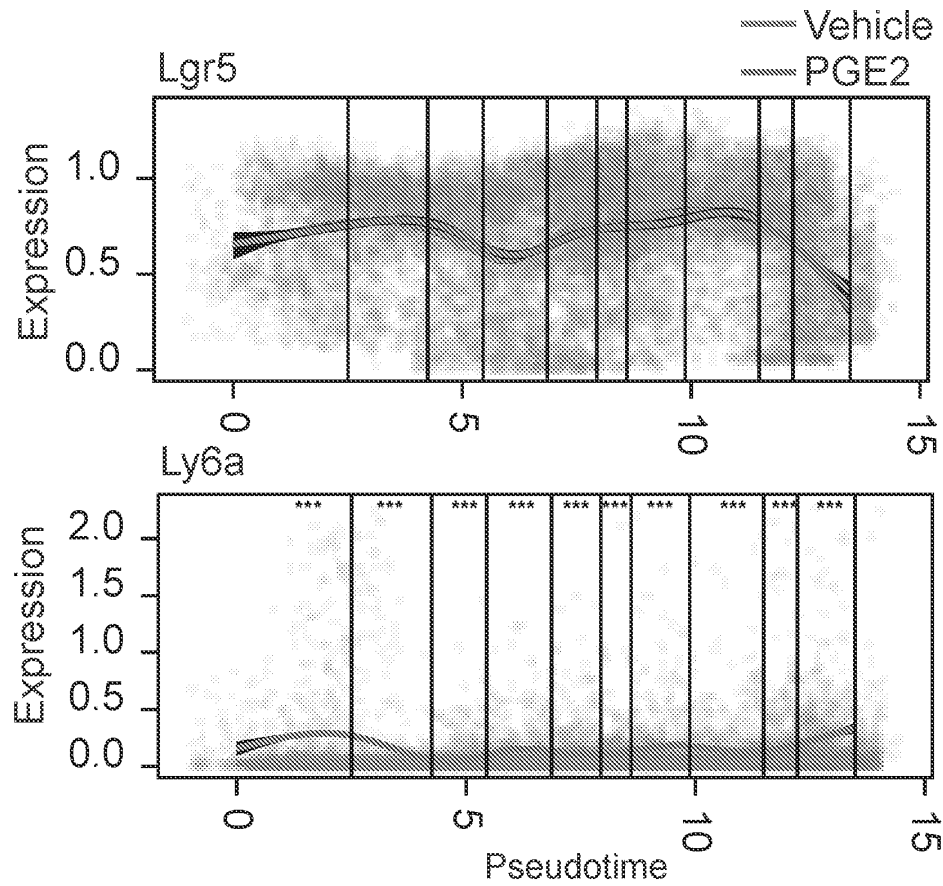


FIG. 13N

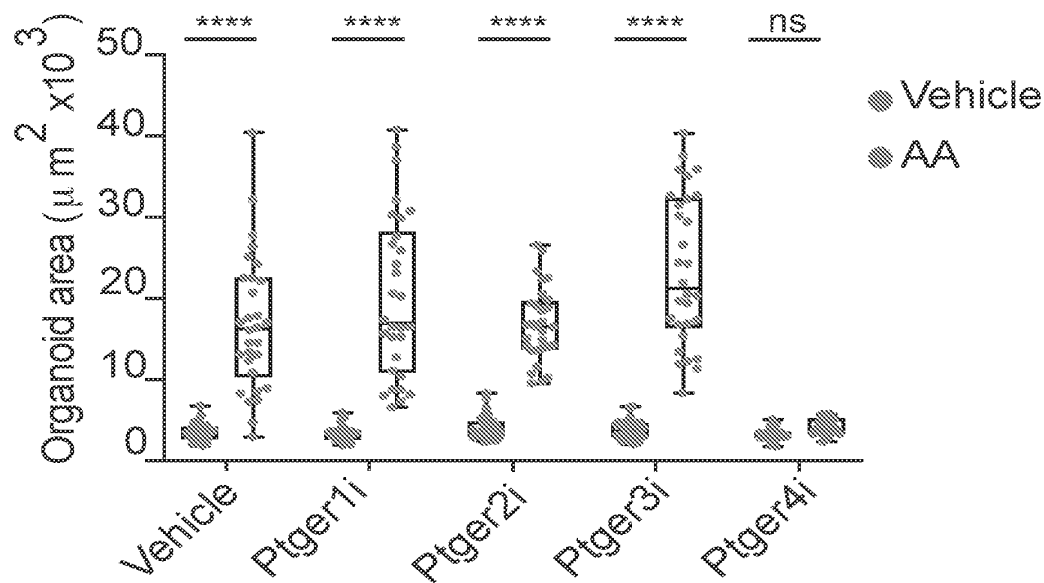


FIG. 14A

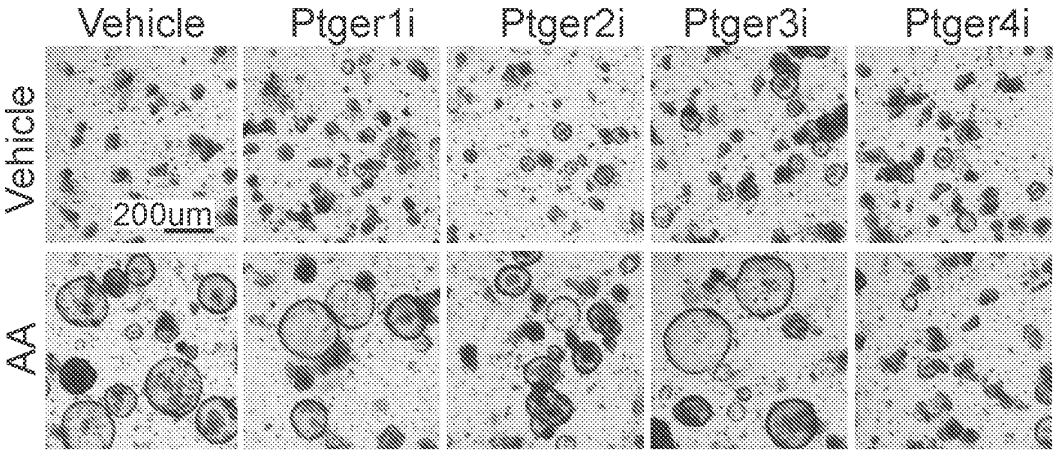


FIG. 14B

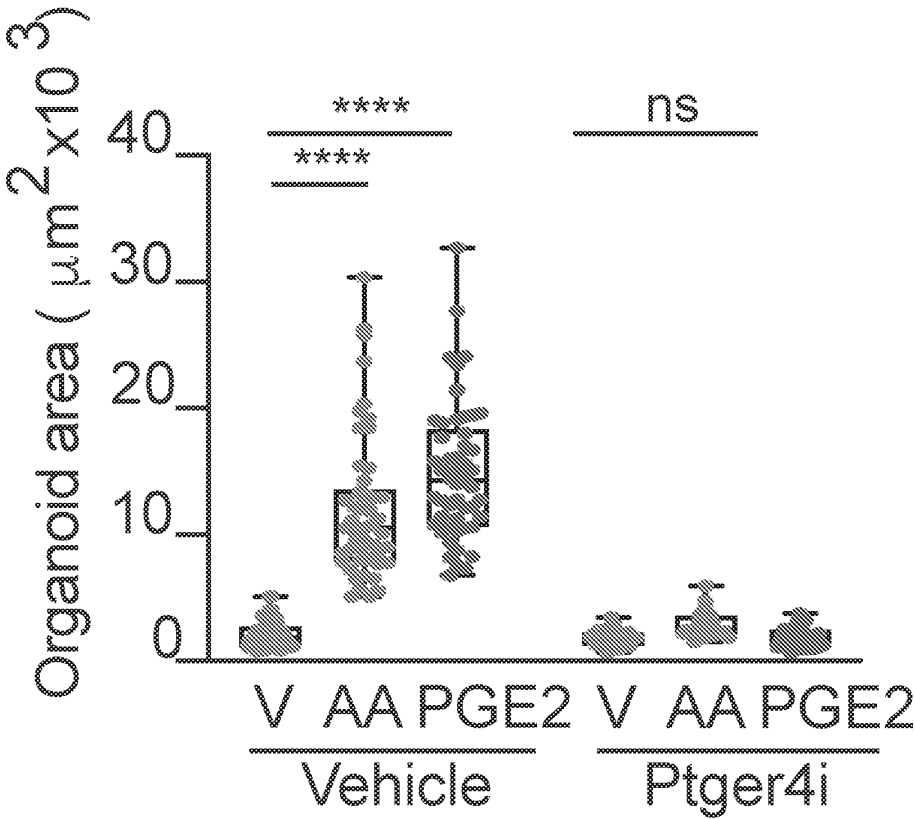


FIG. 14C

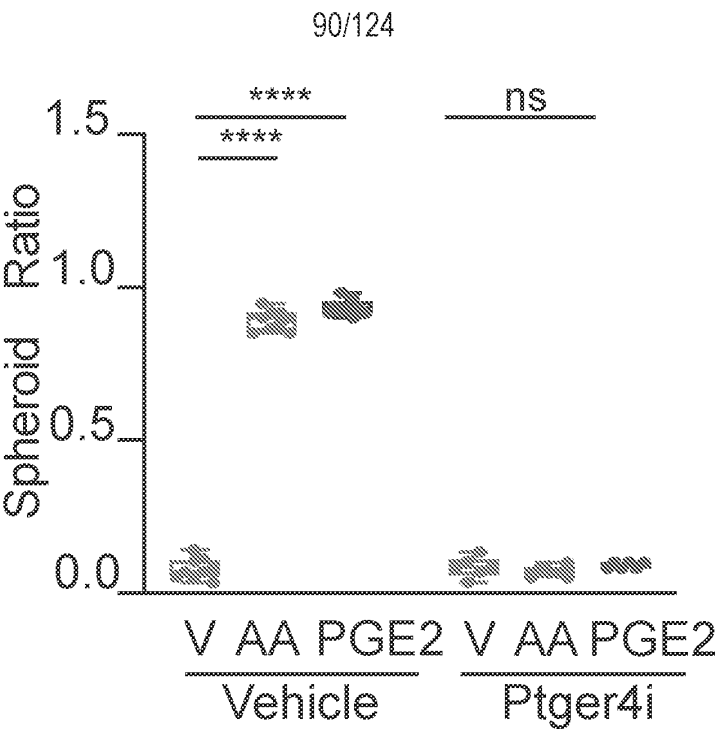


FIG. 14D

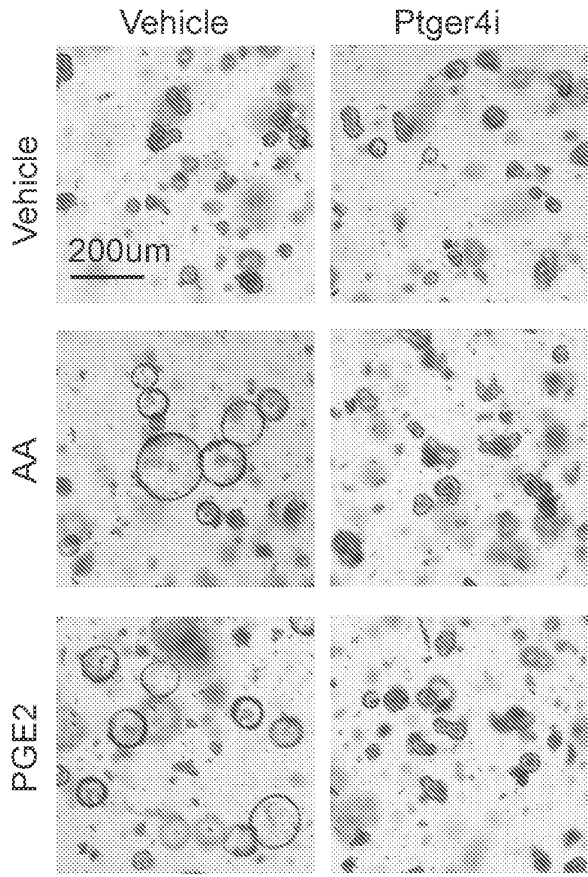


FIG. 14E

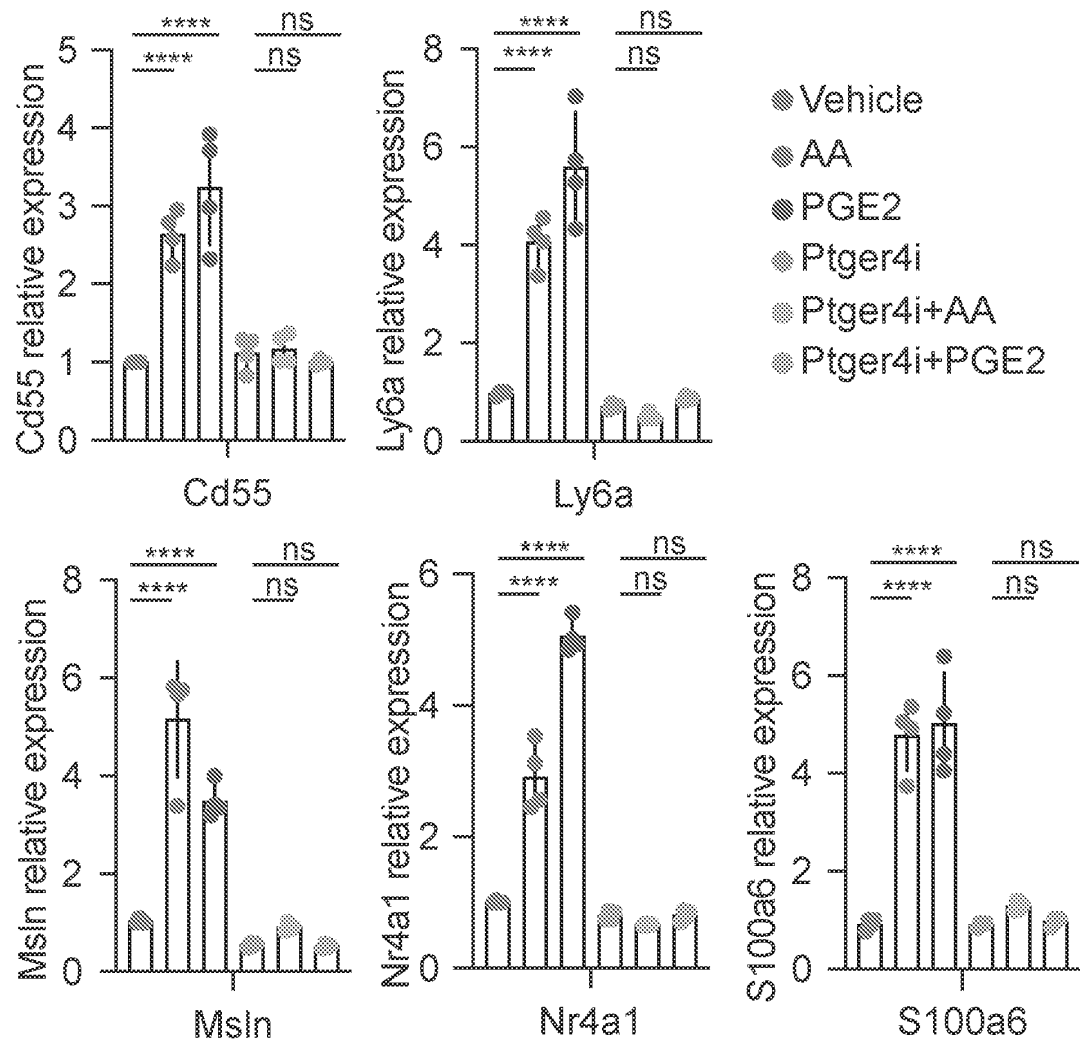


FIG. 14F

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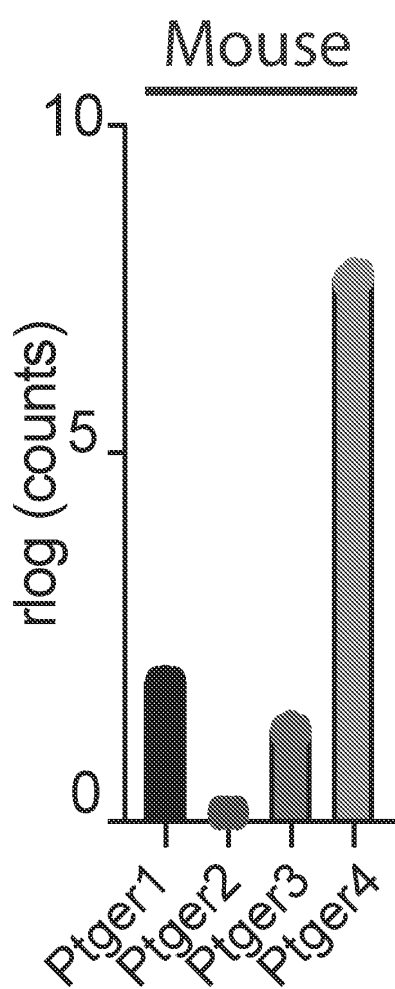


FIG. 14G

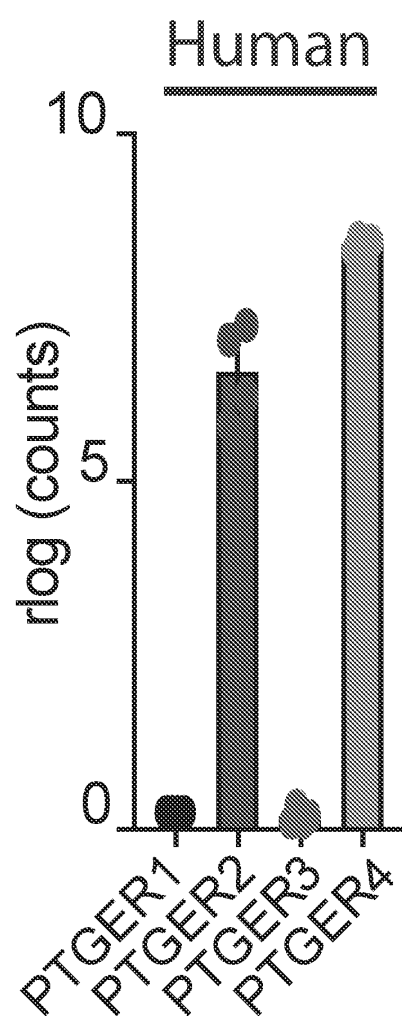


FIG. 14H

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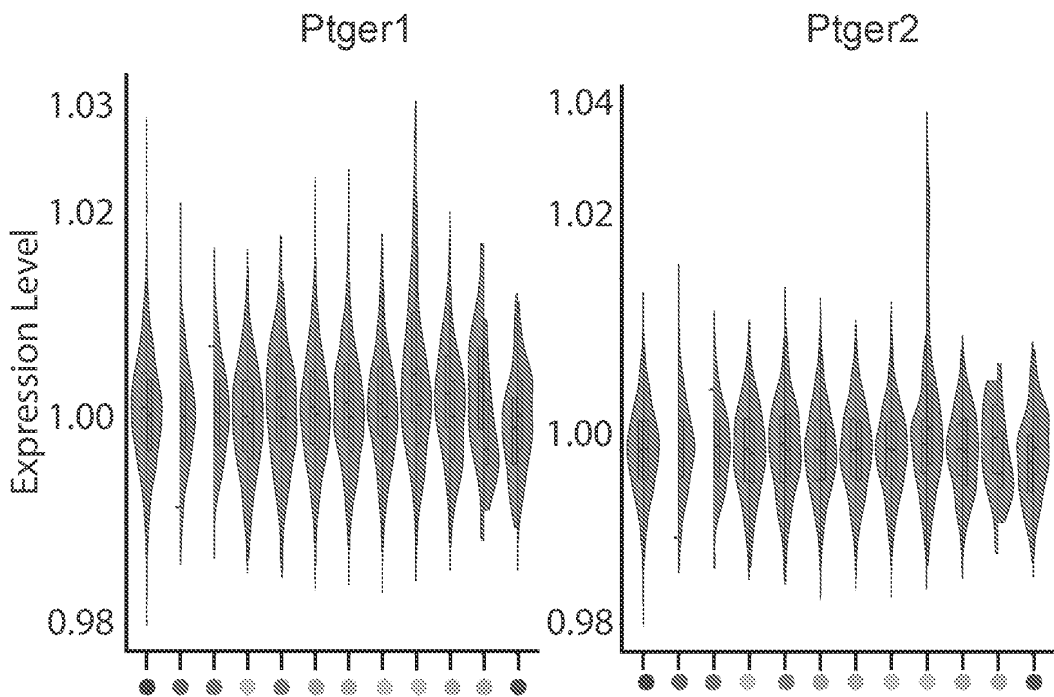
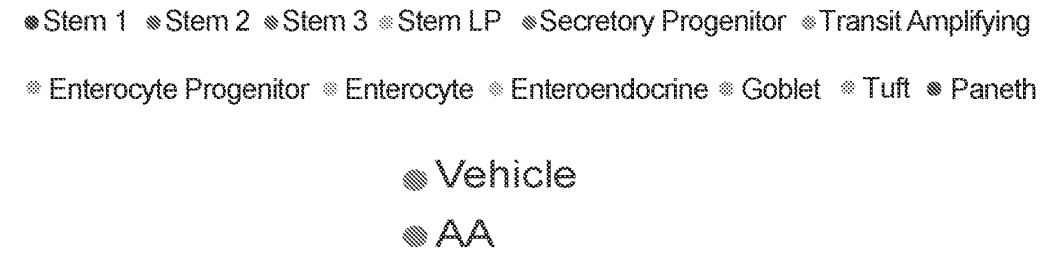


FIG. 14I

FIG. 14J

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- ◆ Stem 1 ◆ Stem 2 ◆ Stem 3 ◆ Stem LP ◆ Secretory Progenitor ◆ Transit Amplifying
- ◆ Enterocyte Progenitor ◆ Enterocyte ◆ Enteroendocrine ◆ Goblet ◆ Tuft ◆ Paneth
- Vehicle
- AA

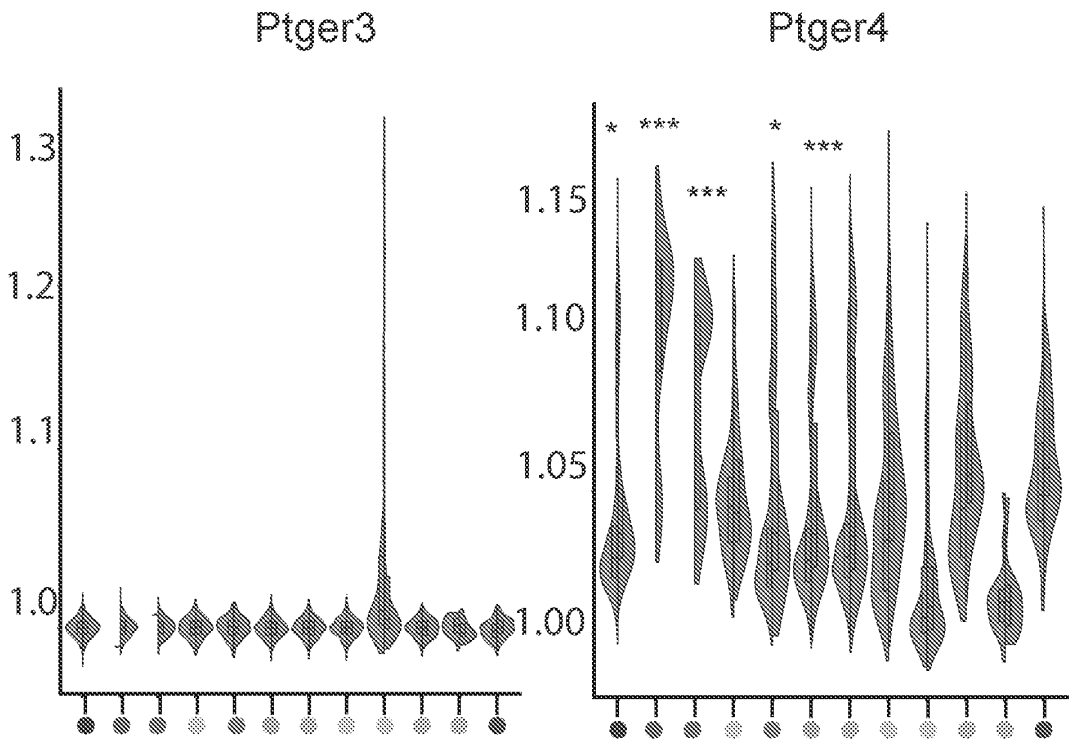


FIG. 14K

FIG. 14L

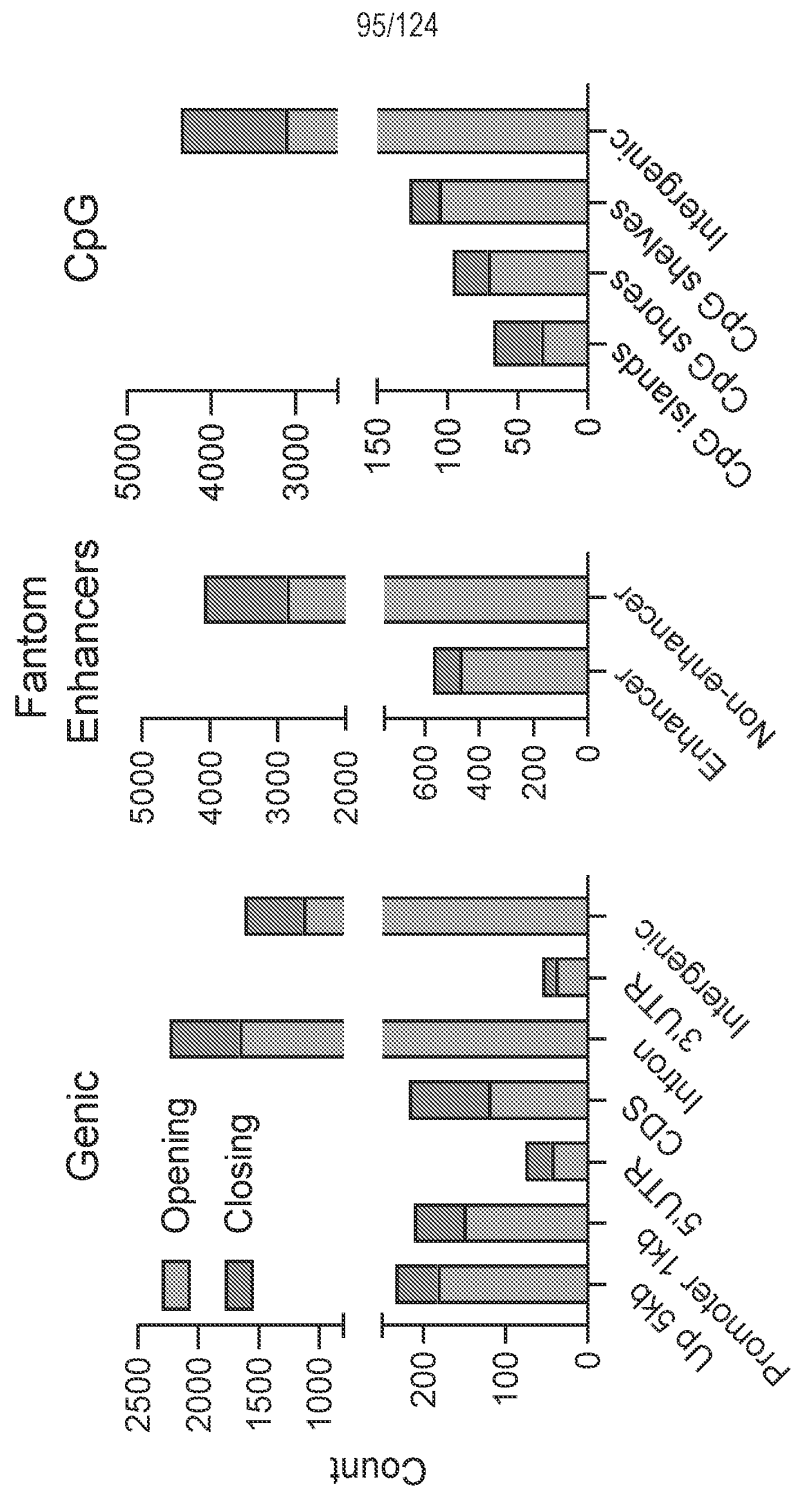


FIG. 15A

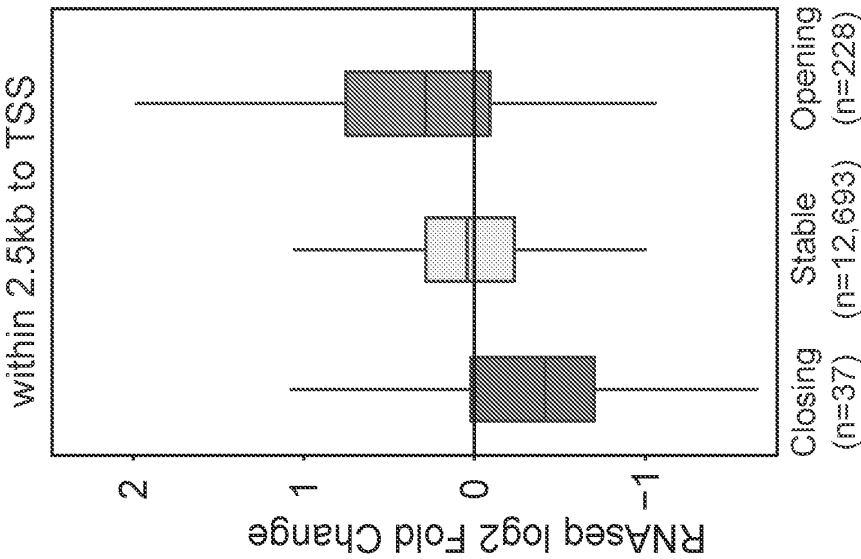


FIG. 15B

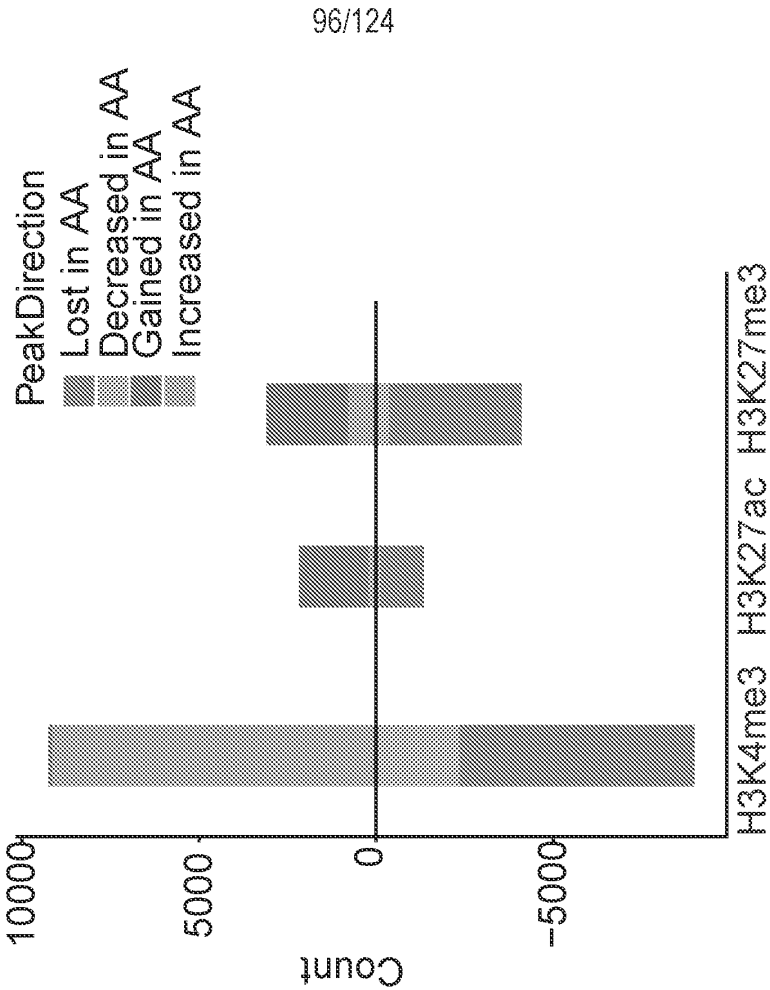


FIG. 15C

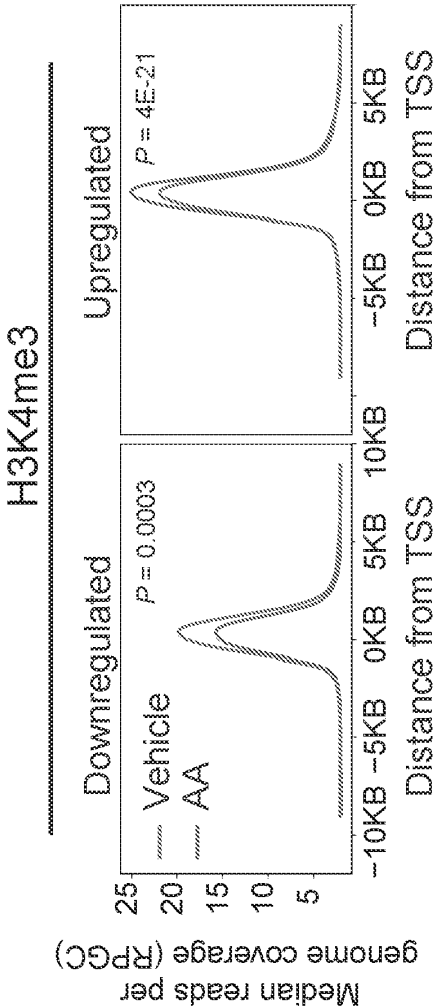


FIG. 15D

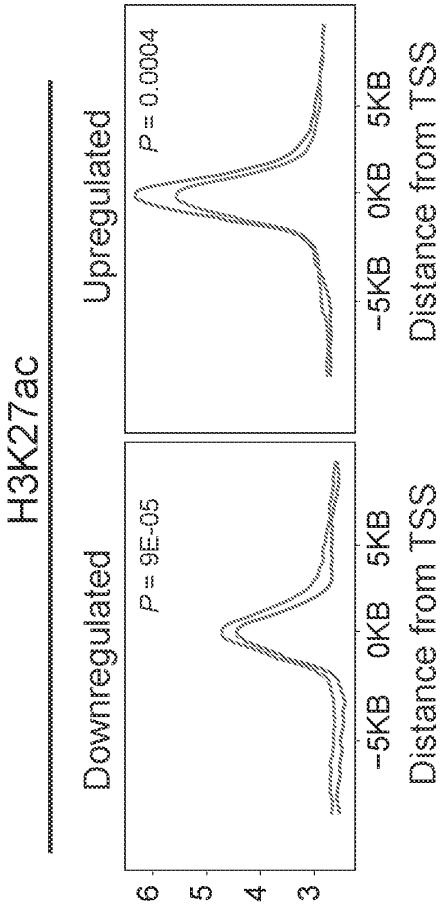


FIG. 15E

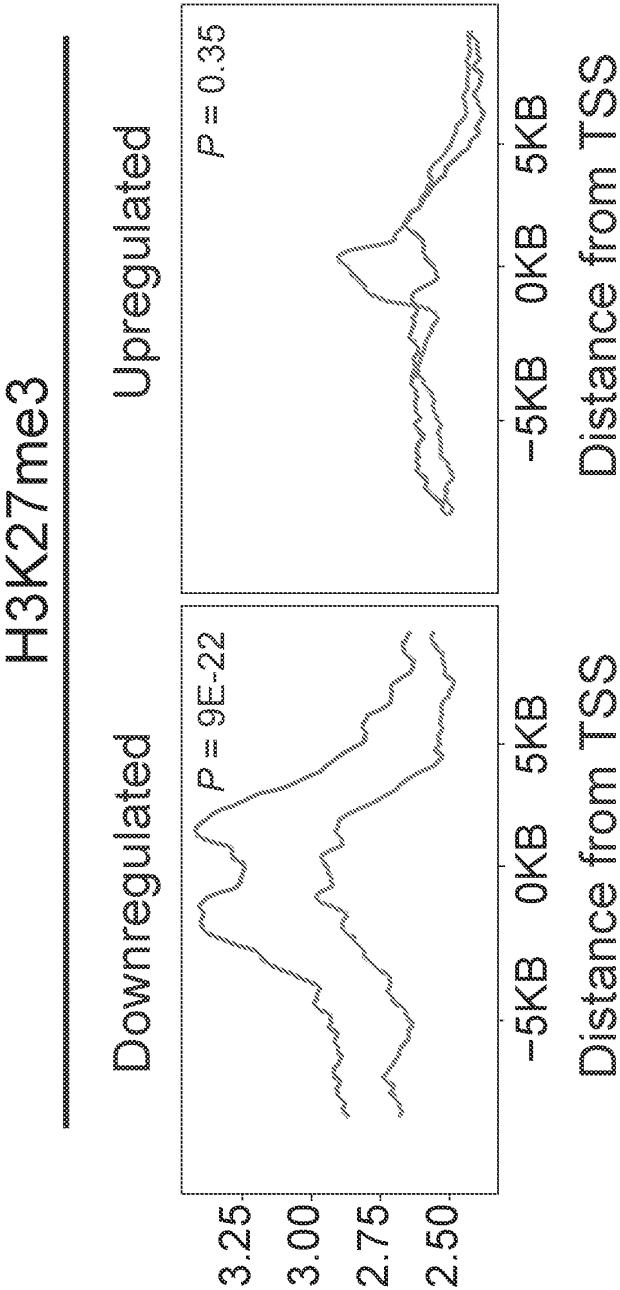
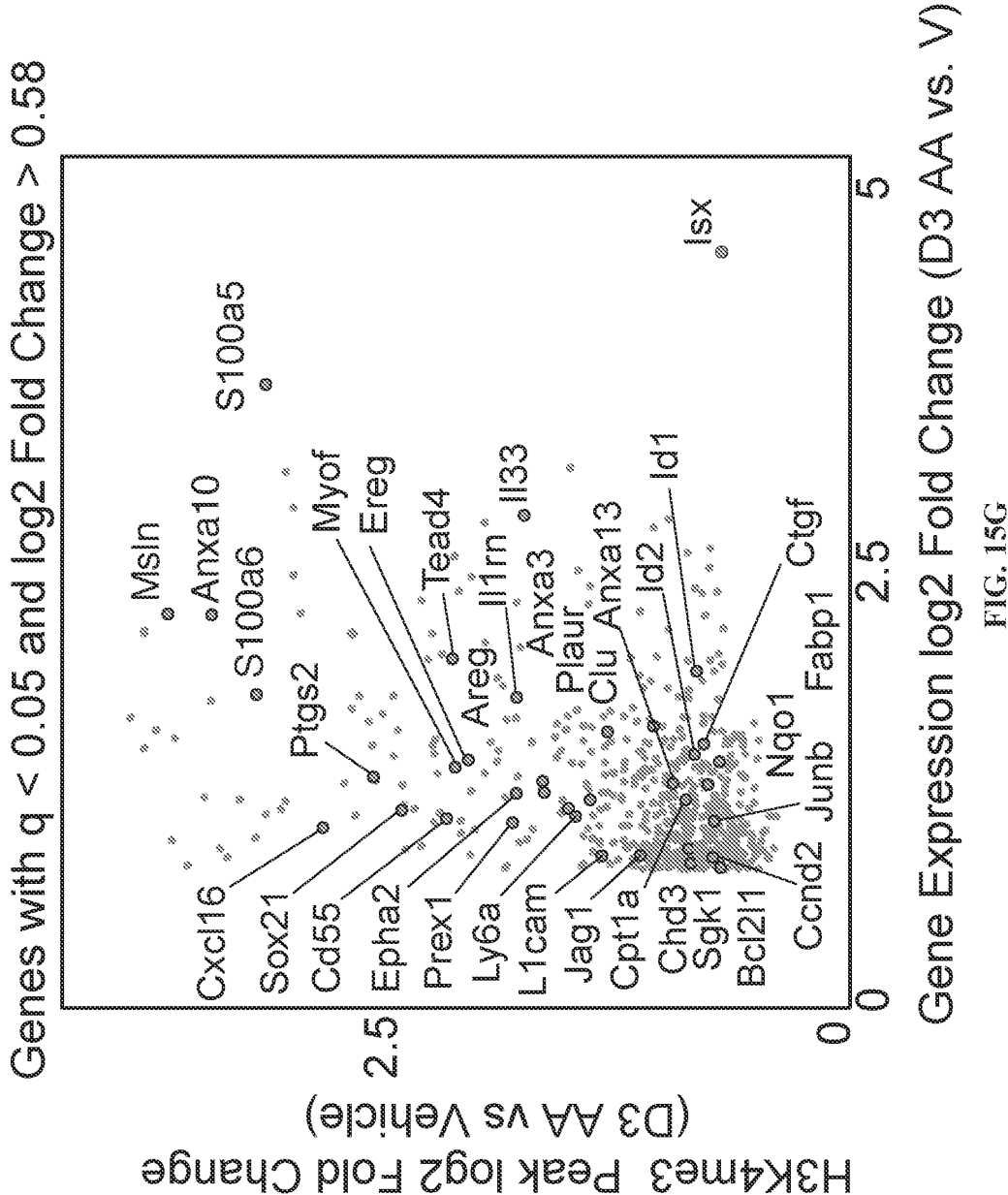


FIG. 15F



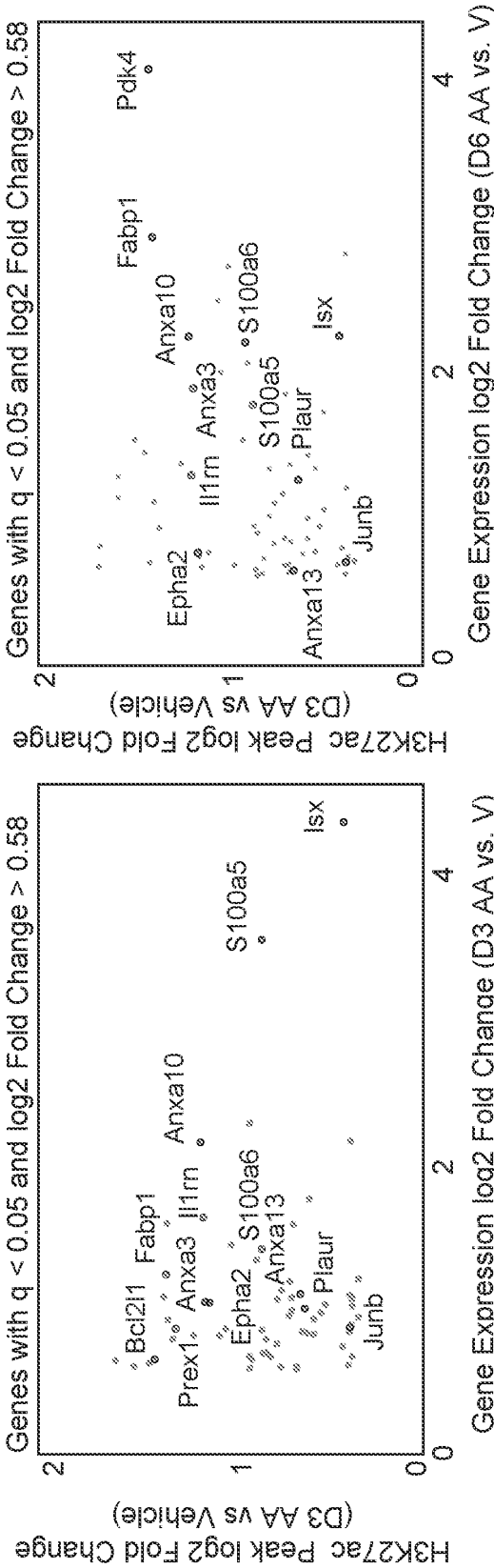


FIG. 15H

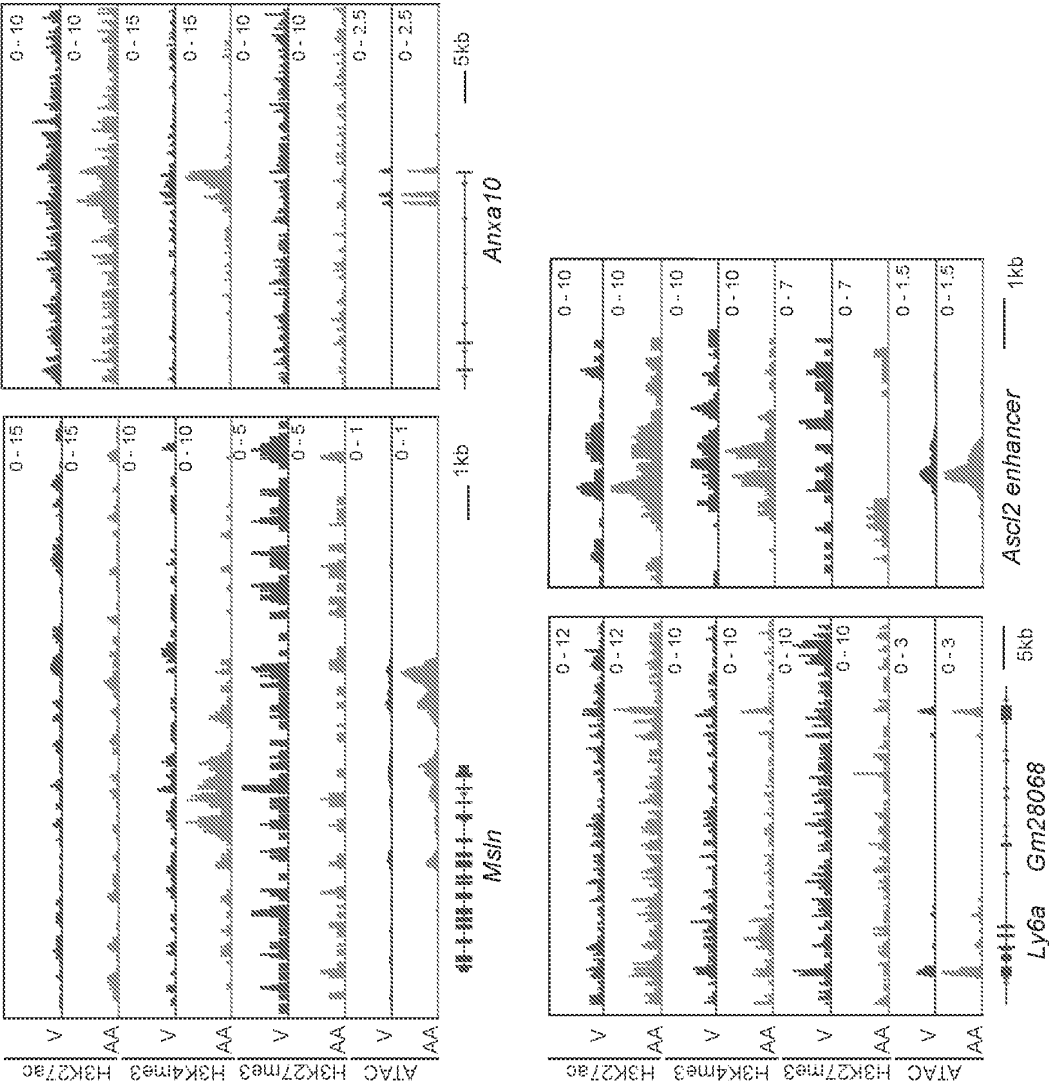


FIG. 15I

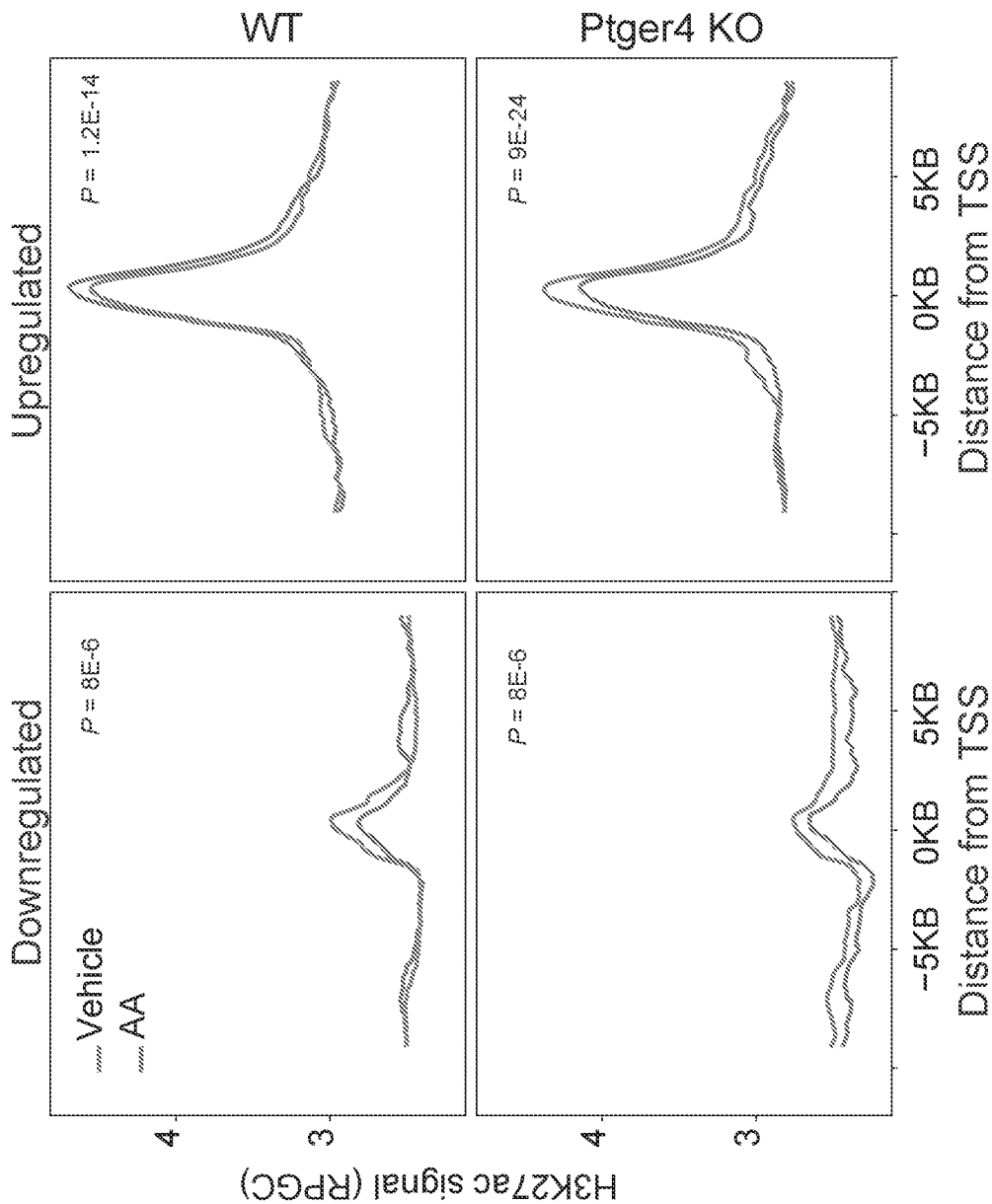


FIG. 15J

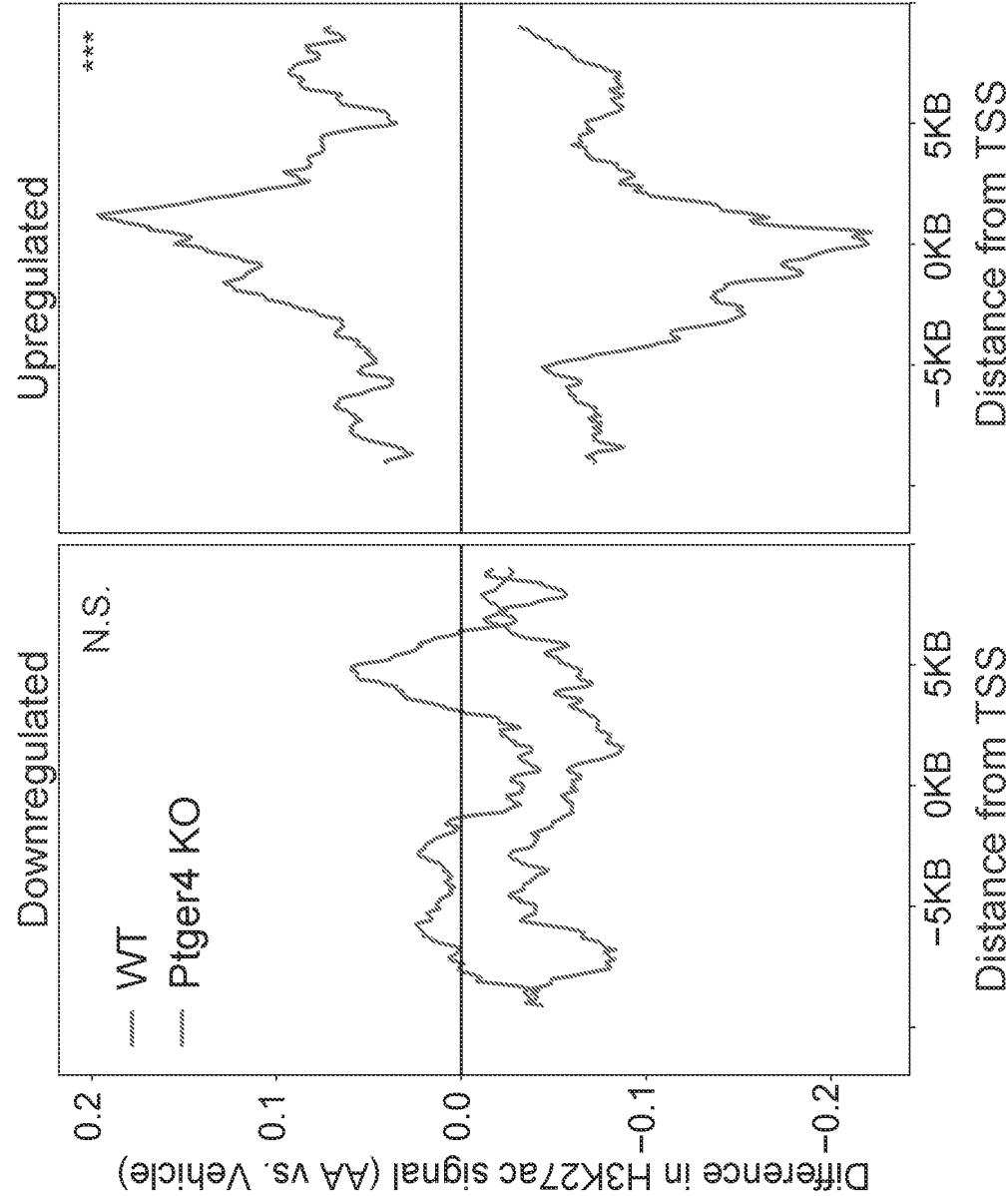


FIG. 15K

Mice, in vivo

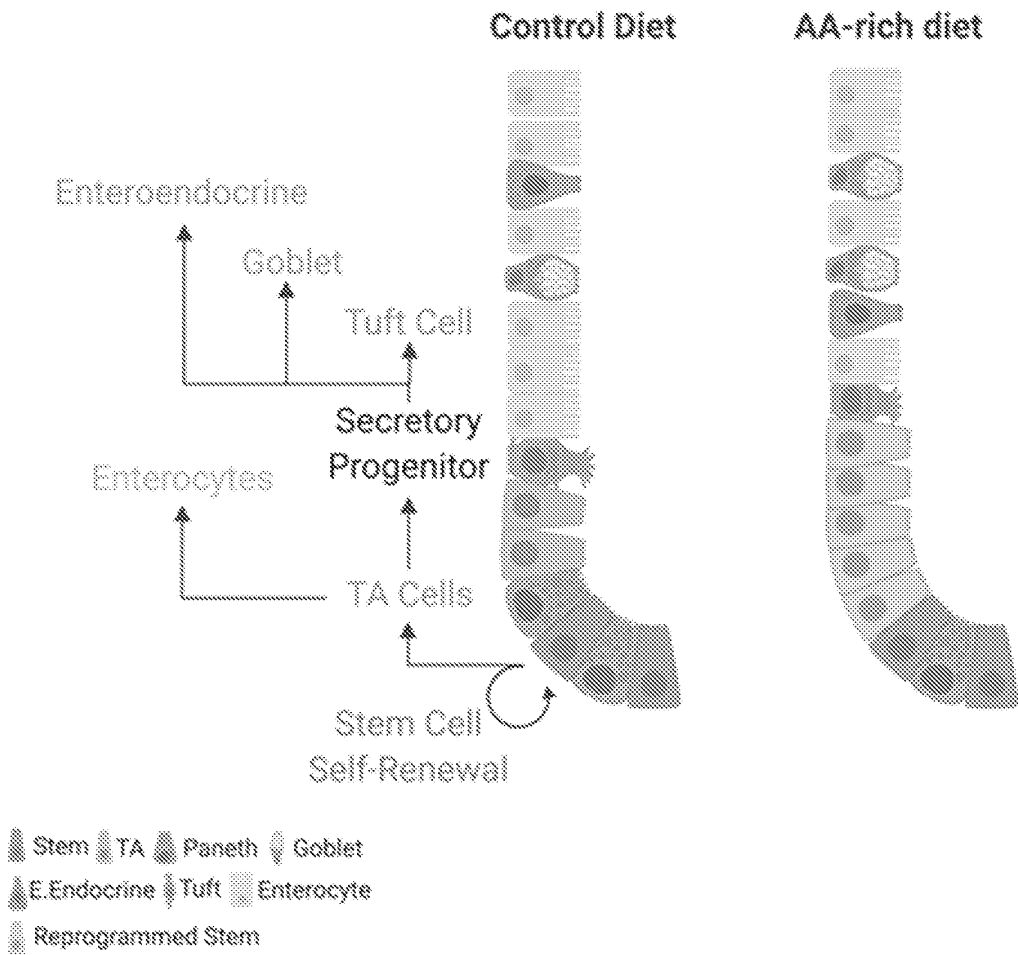


FIG. 16A

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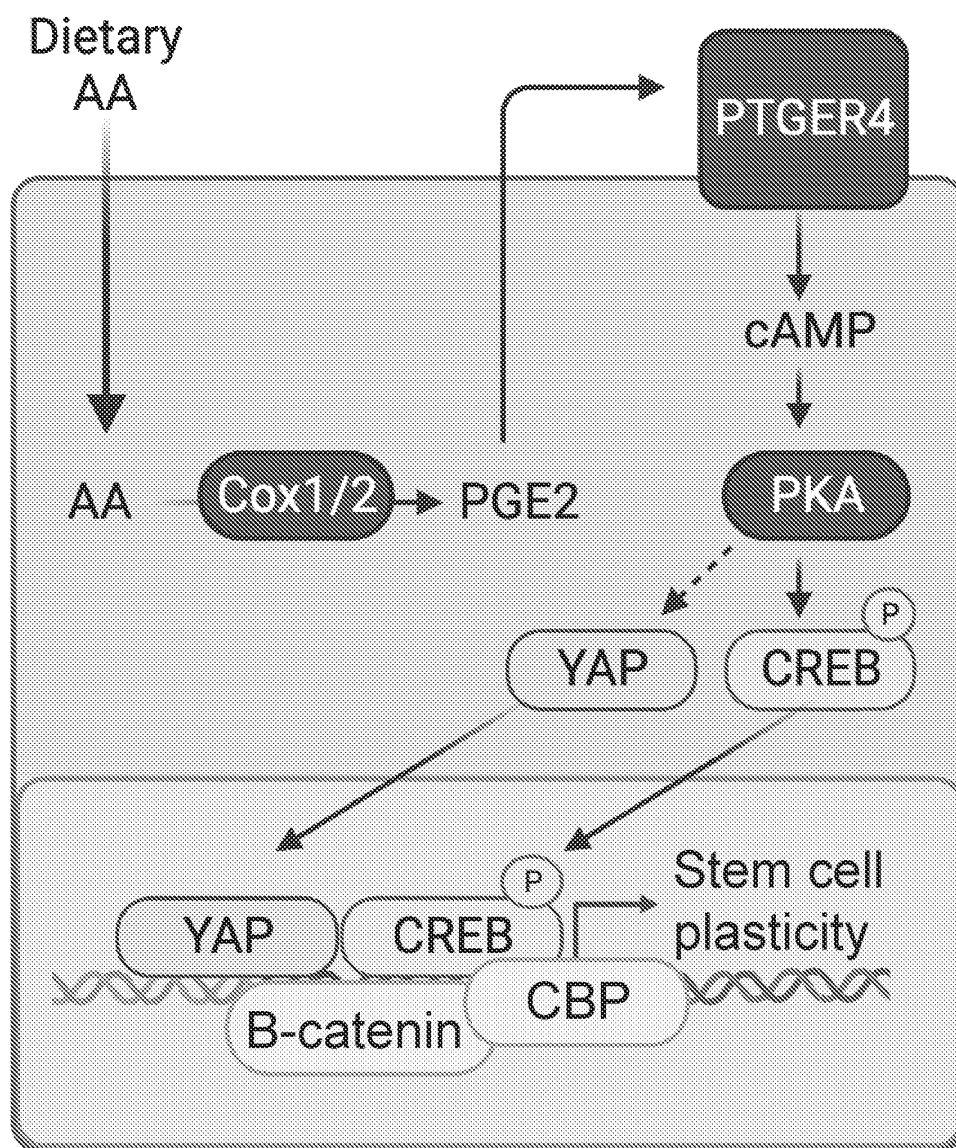


FIG. 16B

Mice and Humans
Organoids, in vitro

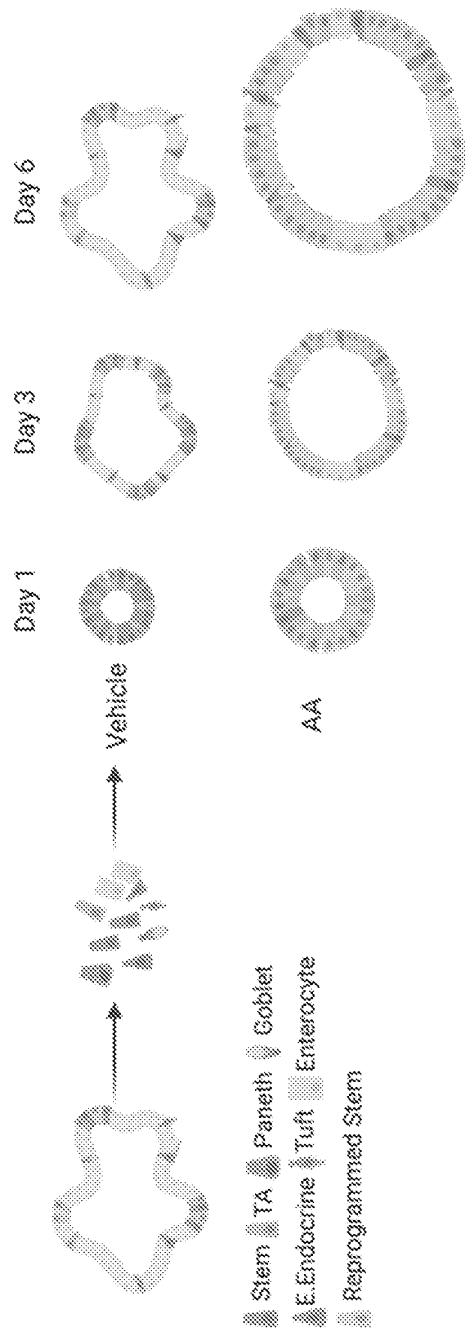


FIG. 16C

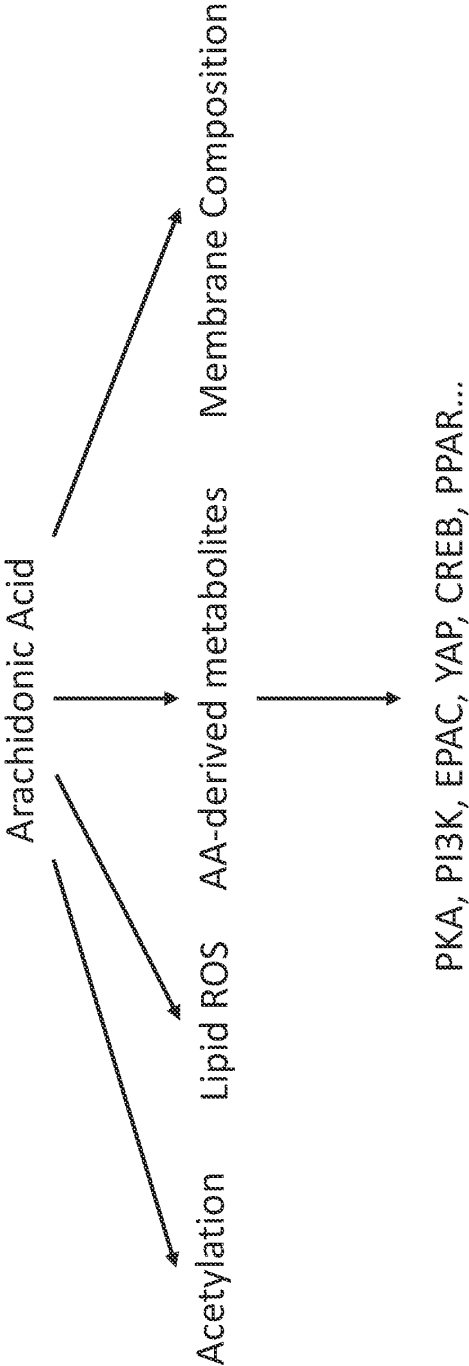
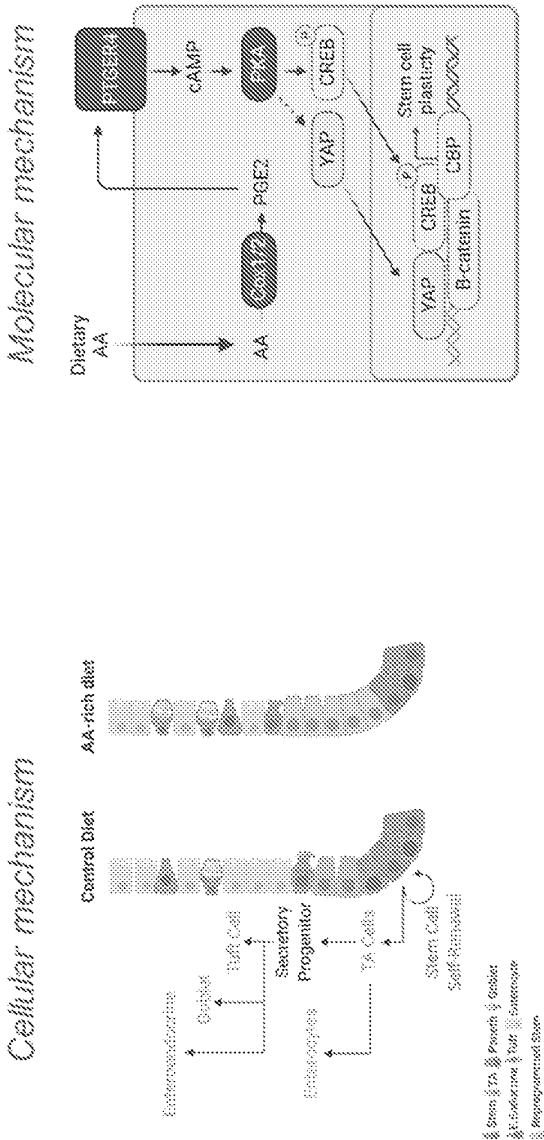


FIG. 16D

A single fatty acid elevation in diet evokes stem cell plasticity that boosts regeneration in the intestine through epigenetic reprogramming



- ✓ Phenotypic organoid screen using fatty acids identified AA as a regenerative nutrient in mouse and human intestinal organoids
- ✓ Causal and conserved metabolic, signaling and epigenetic mechanisms that mediate adaptive dietary AA-induced stem cell reprogramming

Your stem cells are what you eat!

FIG. 16E

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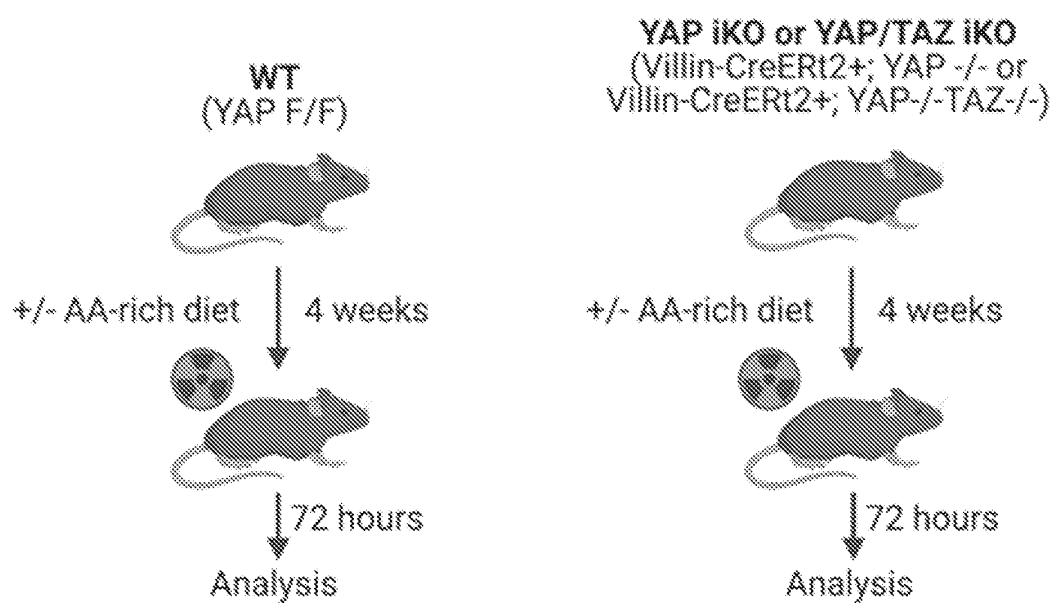
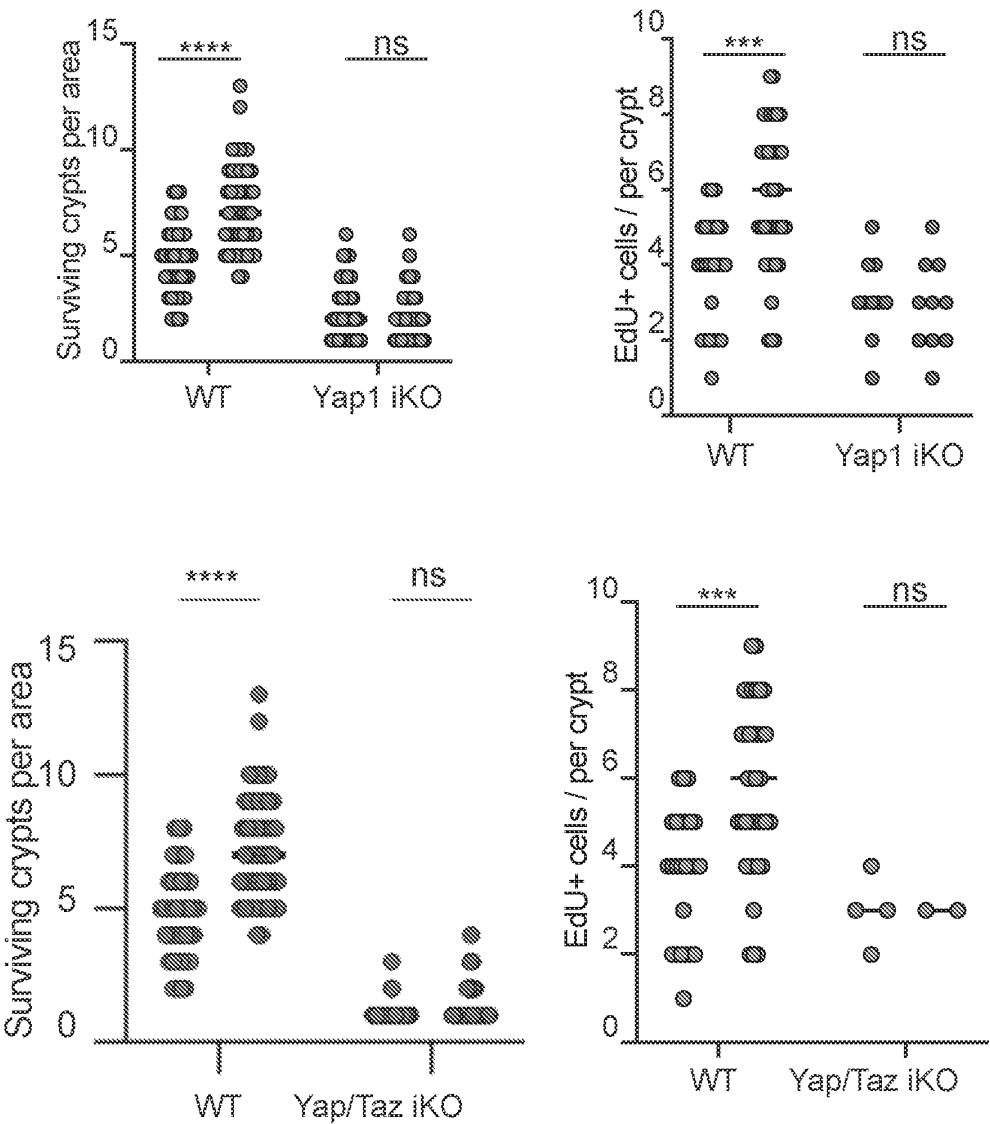


FIG. 17A

YAP pathway is necessary for the regenerative effects of dietary AA

✓ Villin-CreERt2 mice for inducible and conditional deletion of floxed target genes in intestinal epithelial cells



- Control
 - ARD
- ✓ Confirmed the necessity of YAP in AA-induced regeneration phenotype in orthogonal ex vivo assays.

FIG. 17B

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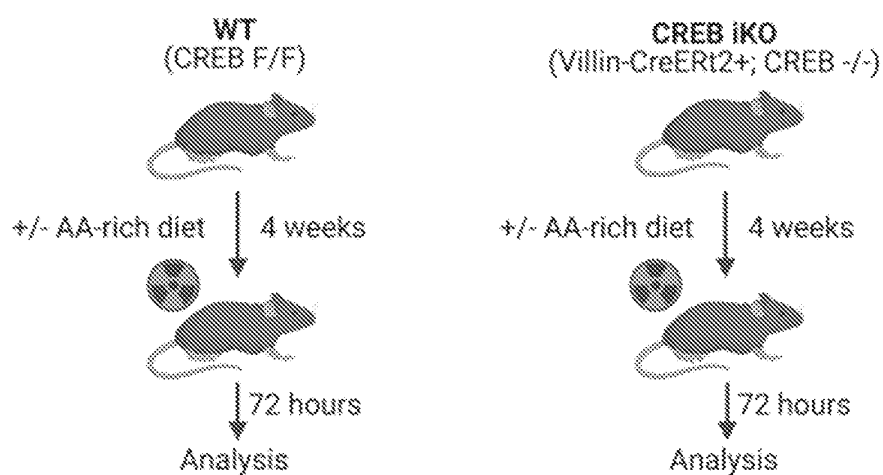
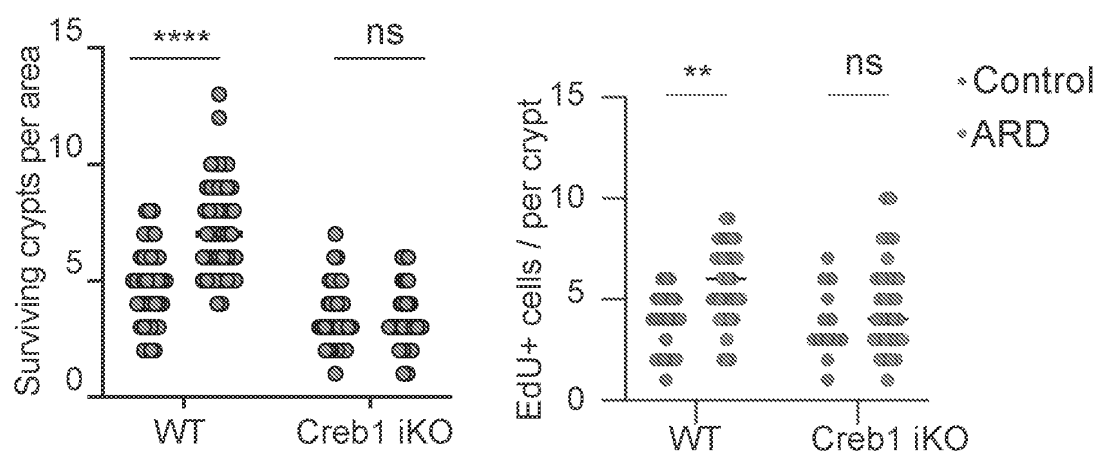


FIG. 17C

CREB1 is necessary for the regenerative effects of dietary AA



- ✓ Confirmed the necessity of CREB1 in AA-induced regeneration phenotype in orthogonal ex vivo and in vivo assays.
- ✓ Characterized CREB1 as a new regulator of intestinal stem cell activity independent of its role in mediating the effects of AA

FIG. 17D

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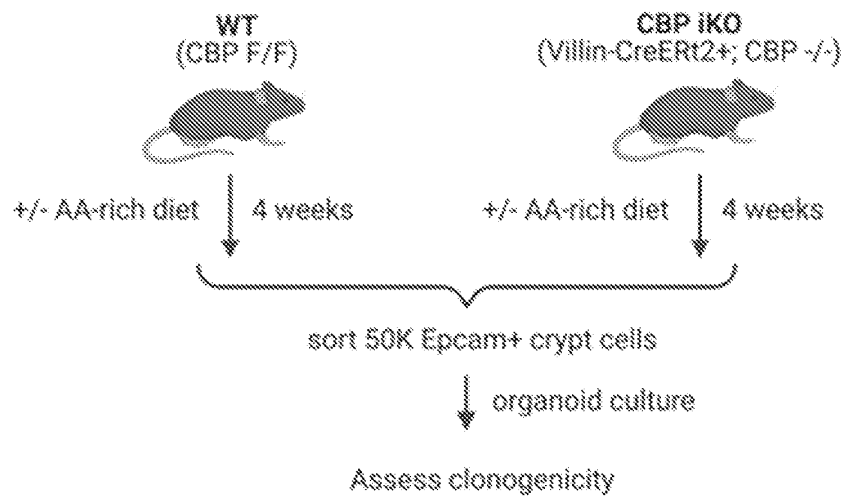
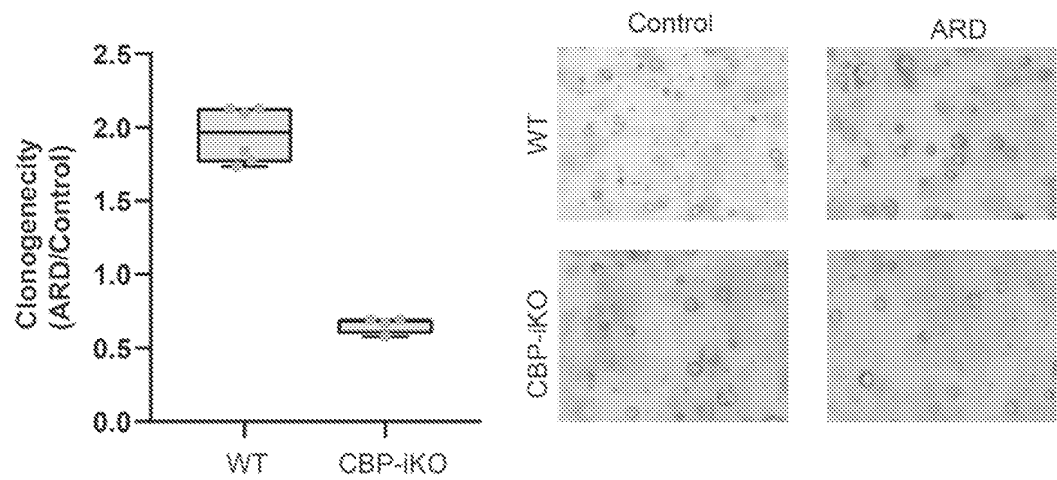


FIG. 17E

CBP is necessary for the regenerative effects of dietary AA



- ✓ Confirmed using pharmacologic inhibitors that prevent CREB-CBP and B-catenin-CBP interactions
- ✓ P300 is not required for AA-induced stemness

FIG. 17F

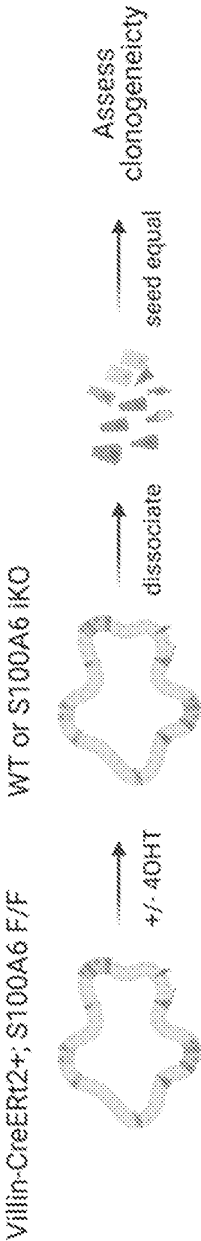


FIG. 18A

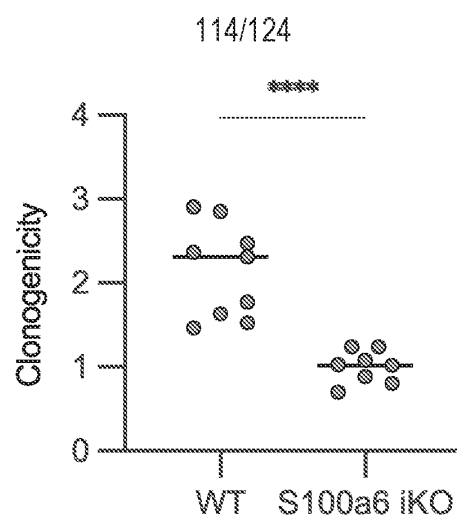
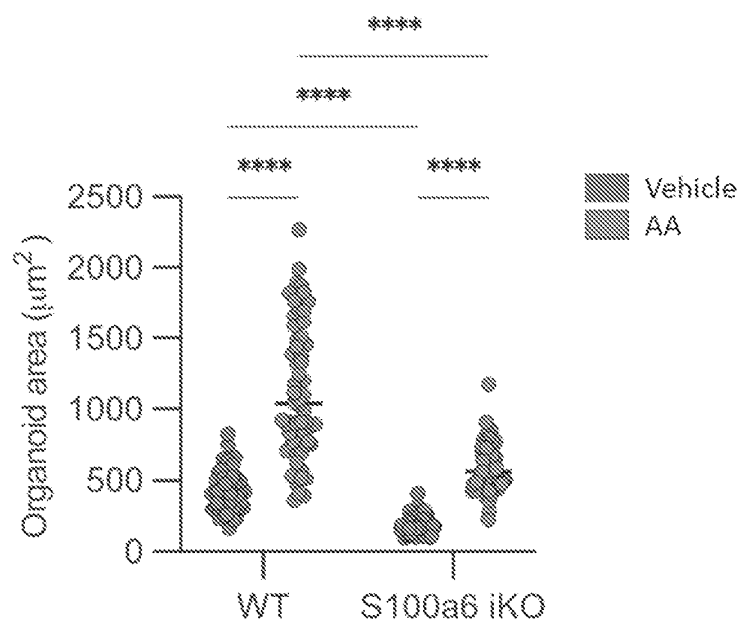


FIG. 18B



S100a6 is a new putative regulator of intestinal stem cell regeneration

FIG. 18C

Clinically relevant tumor-prone mouse model of CRC: mimicking familial adenomatous polyposis patients

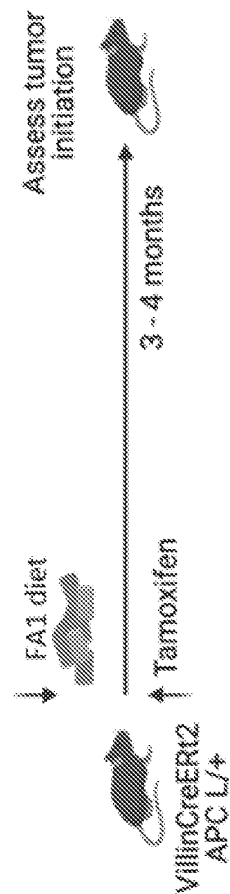


FIG. 19A

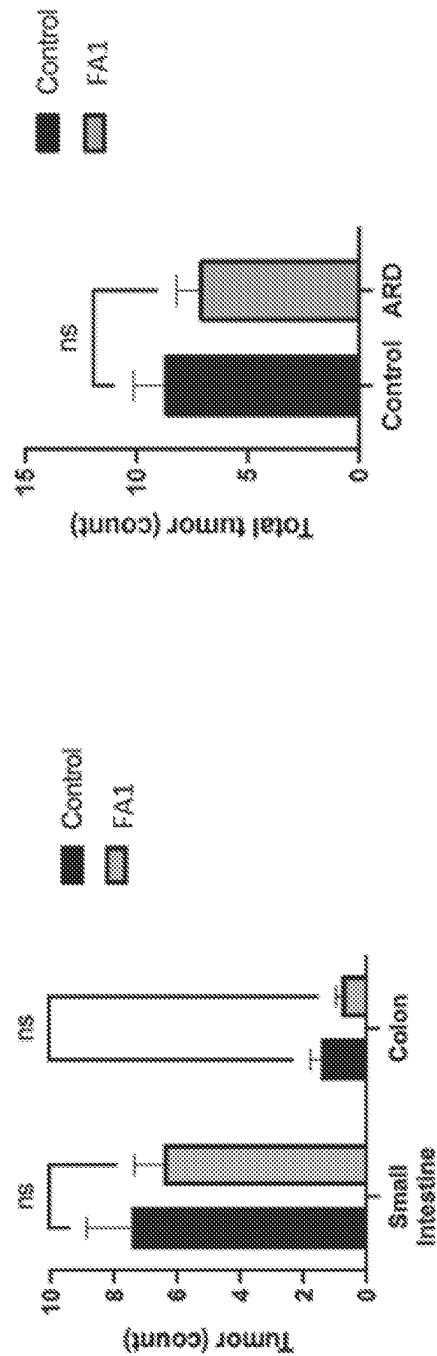
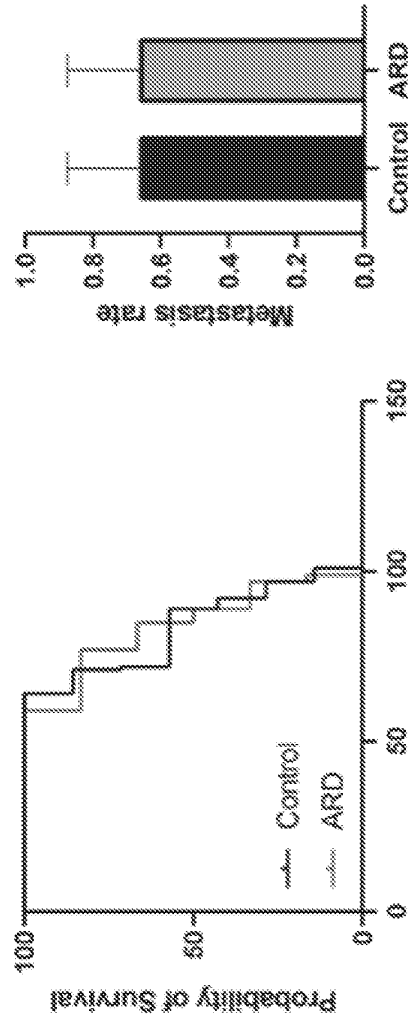
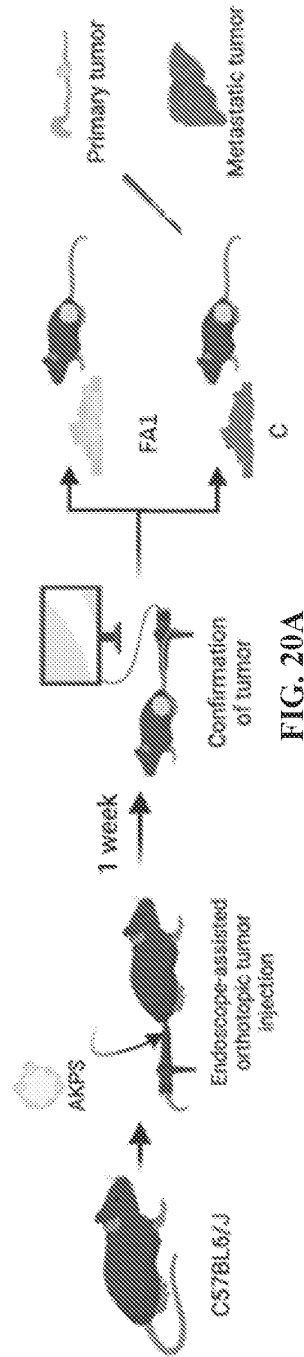


FIG. 19B

FIG. 19C

Clinically relevant tumor progression mouse model: mimicking metastatic colorectal cancer



Time kinetics metabolomics

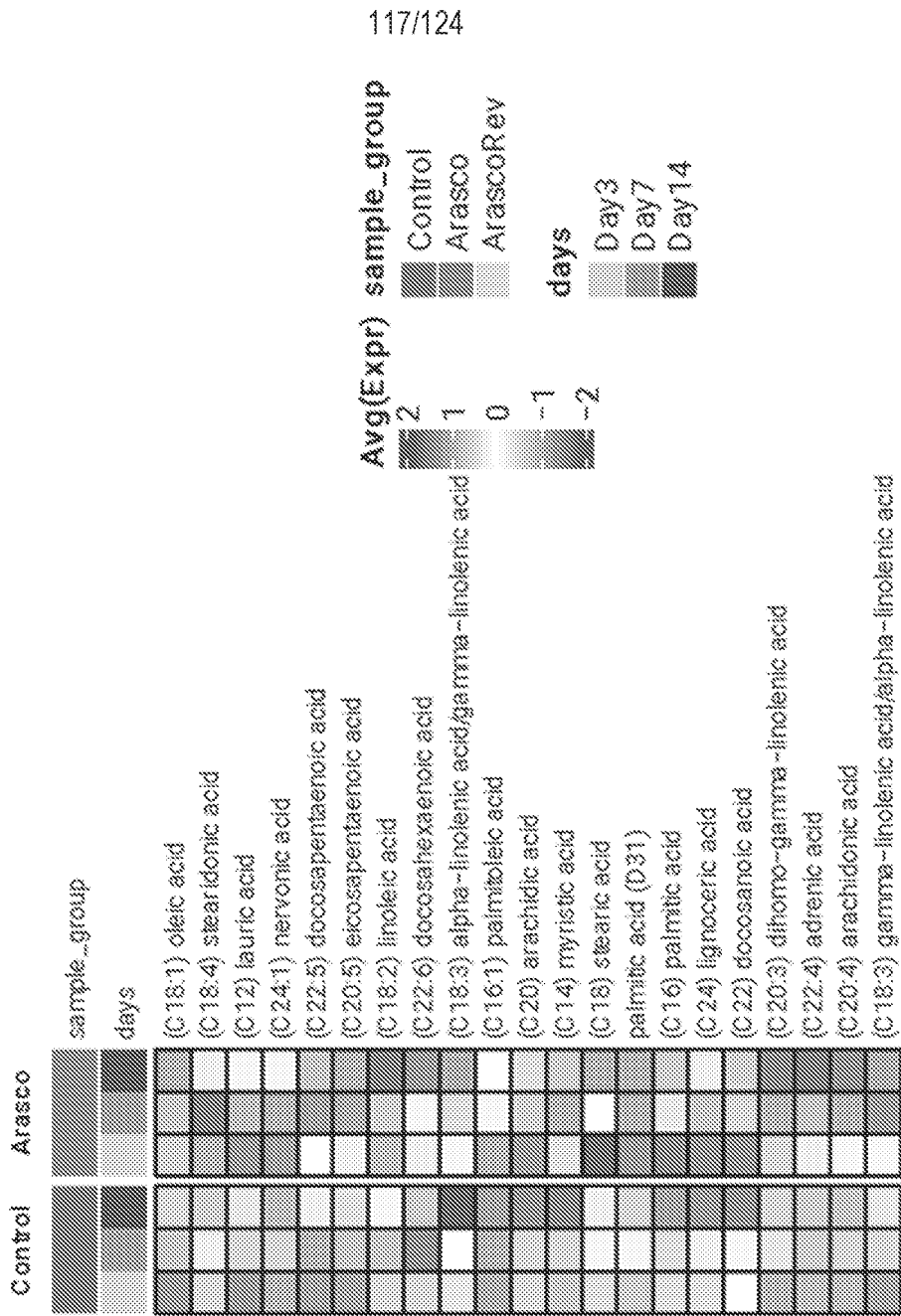


FIG. 21A

Reversal to control diet (2 weeks on 2 weeks off)

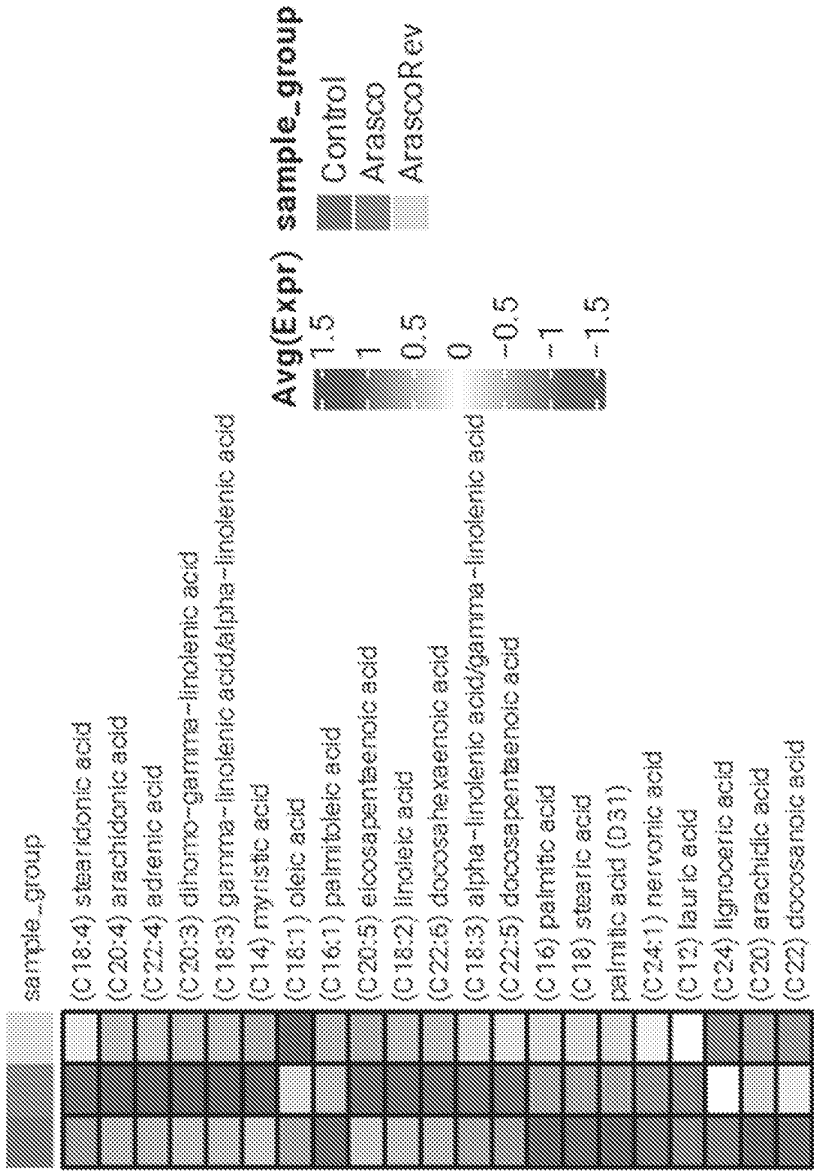


FIG. 21B

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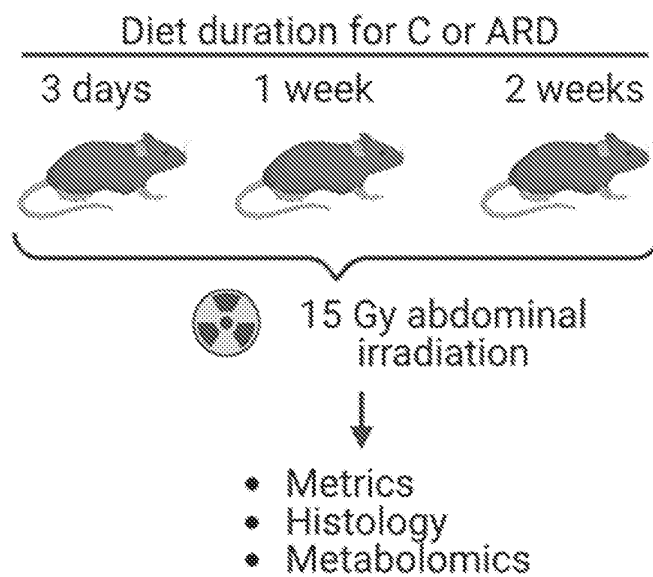


FIG 22A

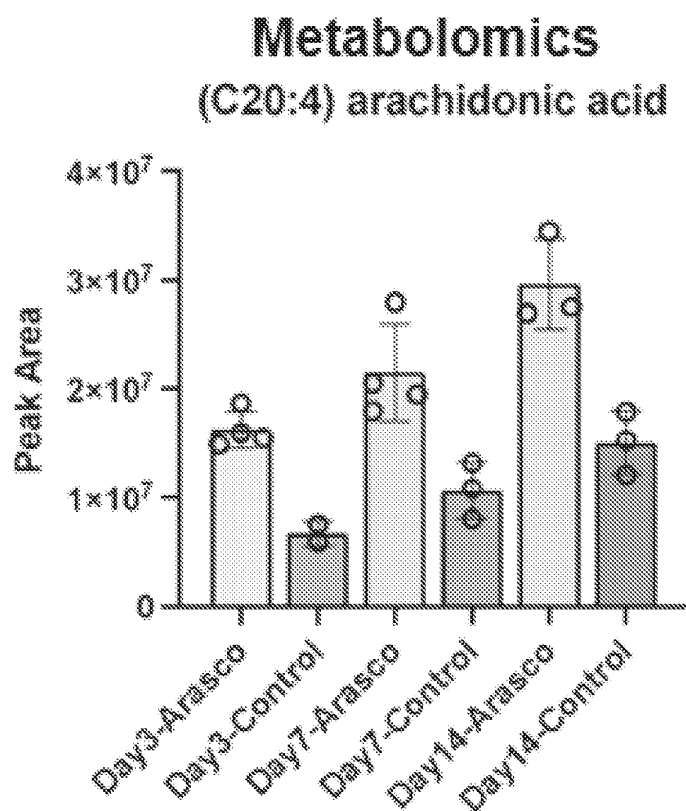


FIG. 22B

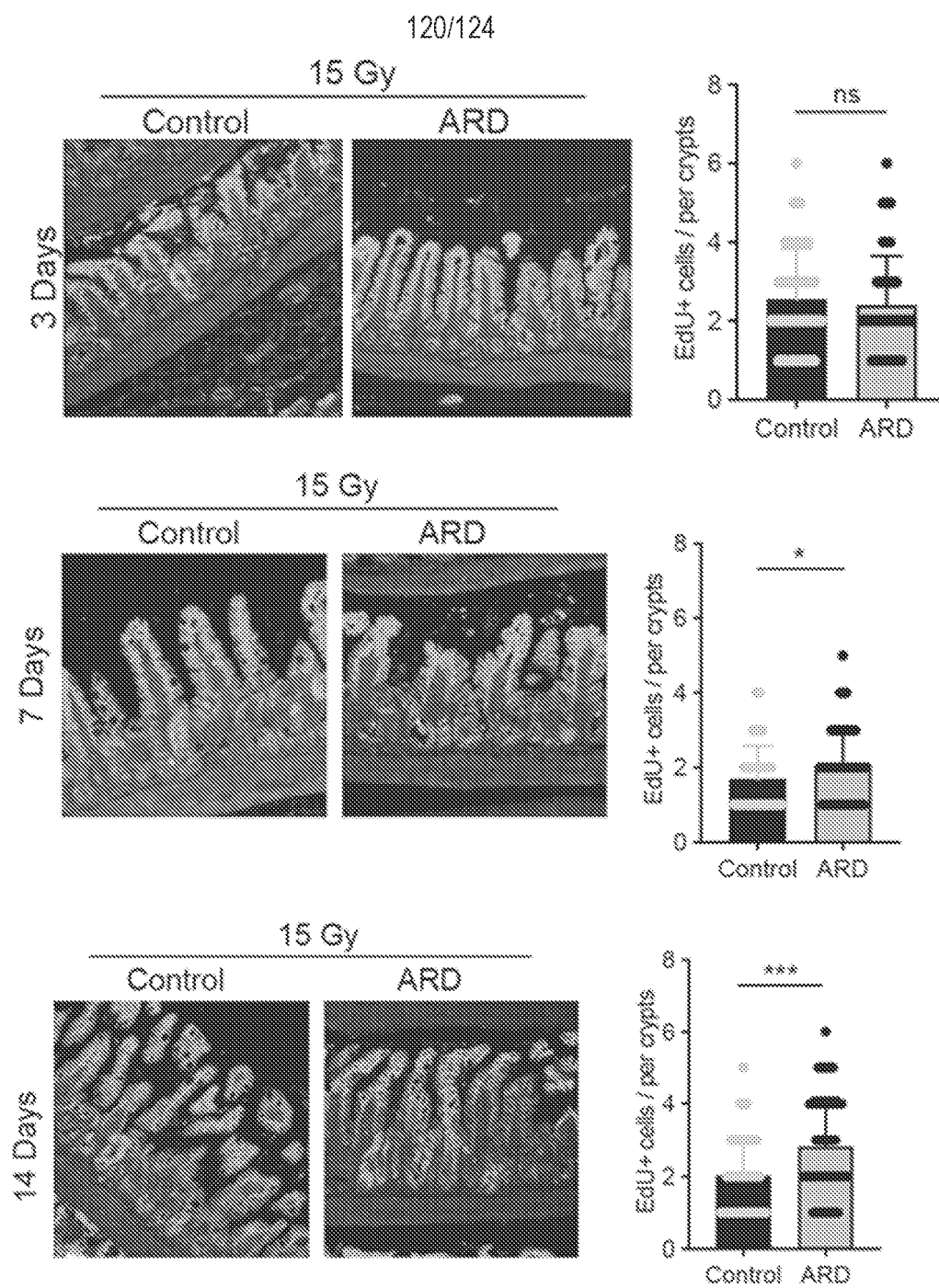


FIG. 22C

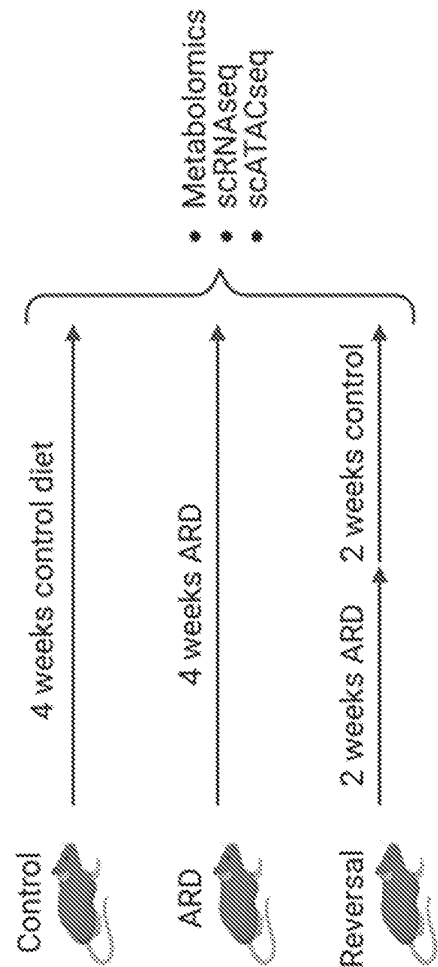


FIG. 23A

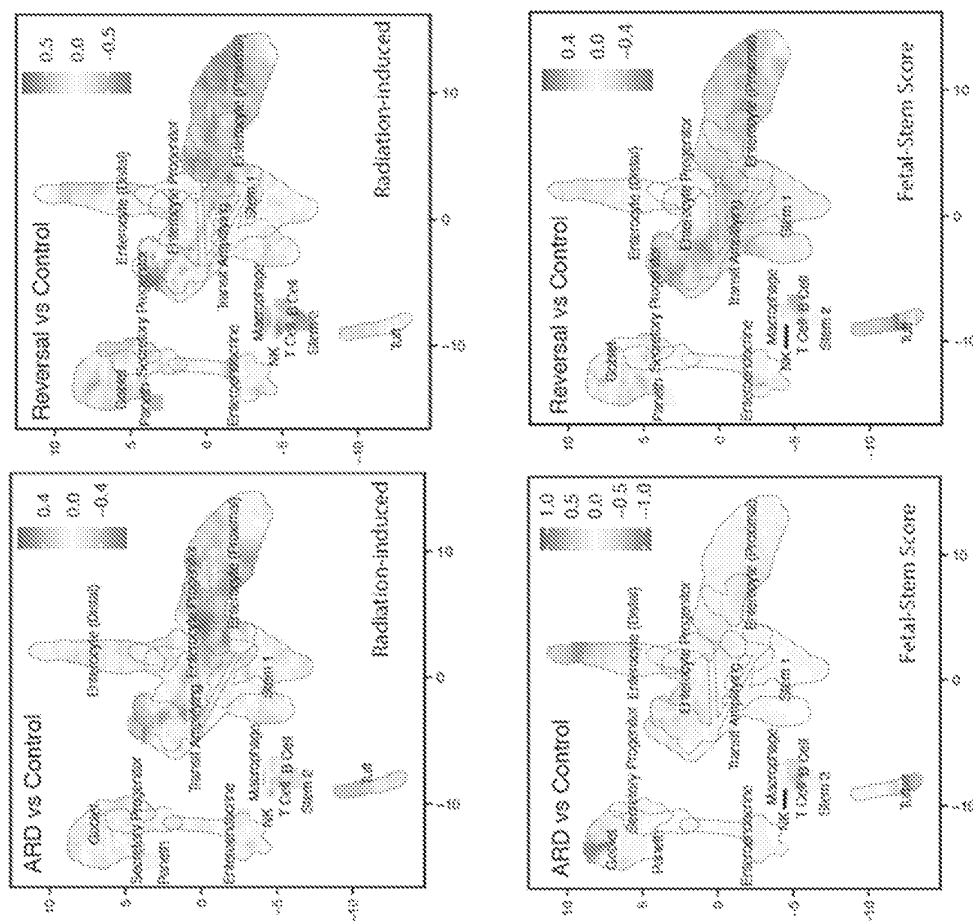


FIG. 23B

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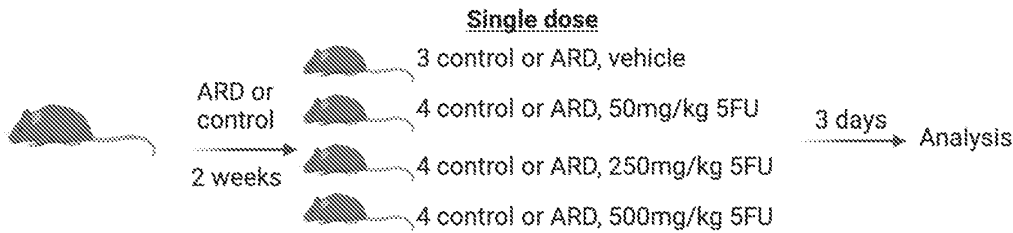


FIG. 24A

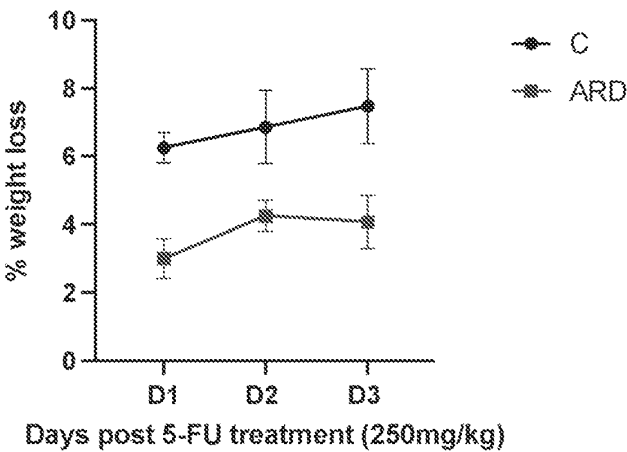


FIG. 24B

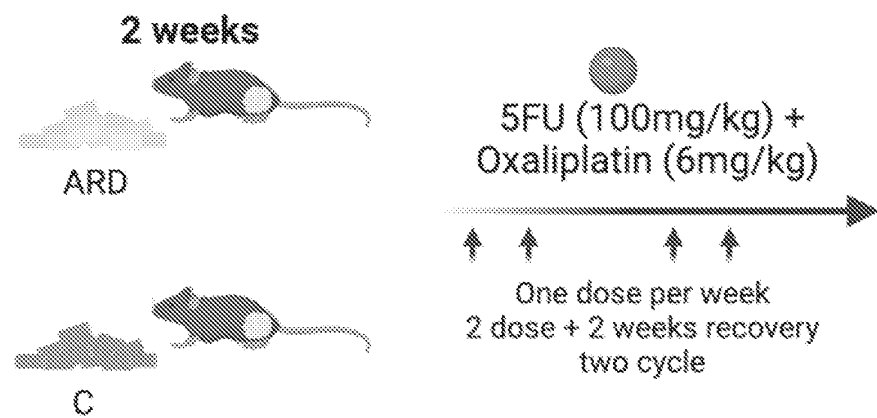


FIG. 25A

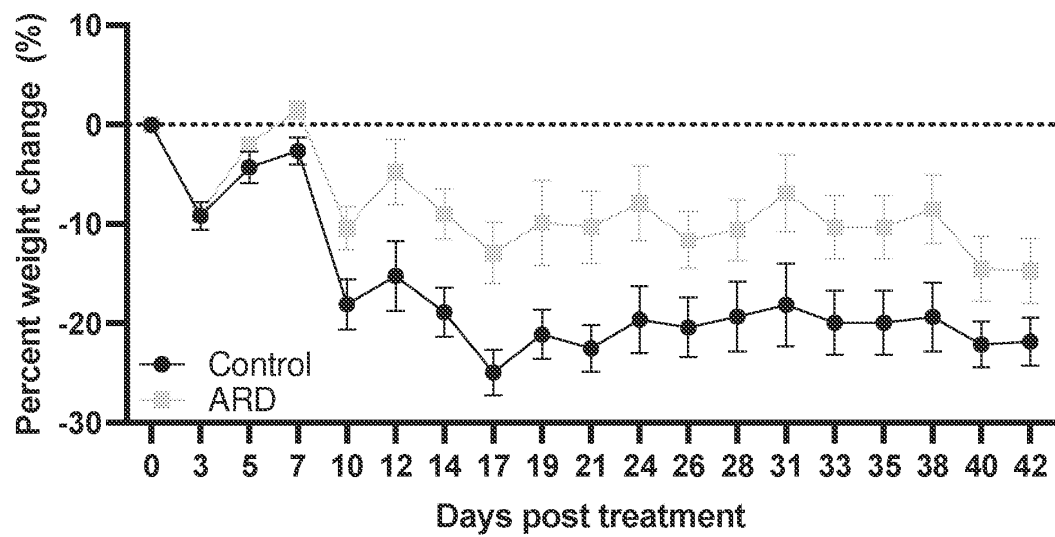


FIG. 25B