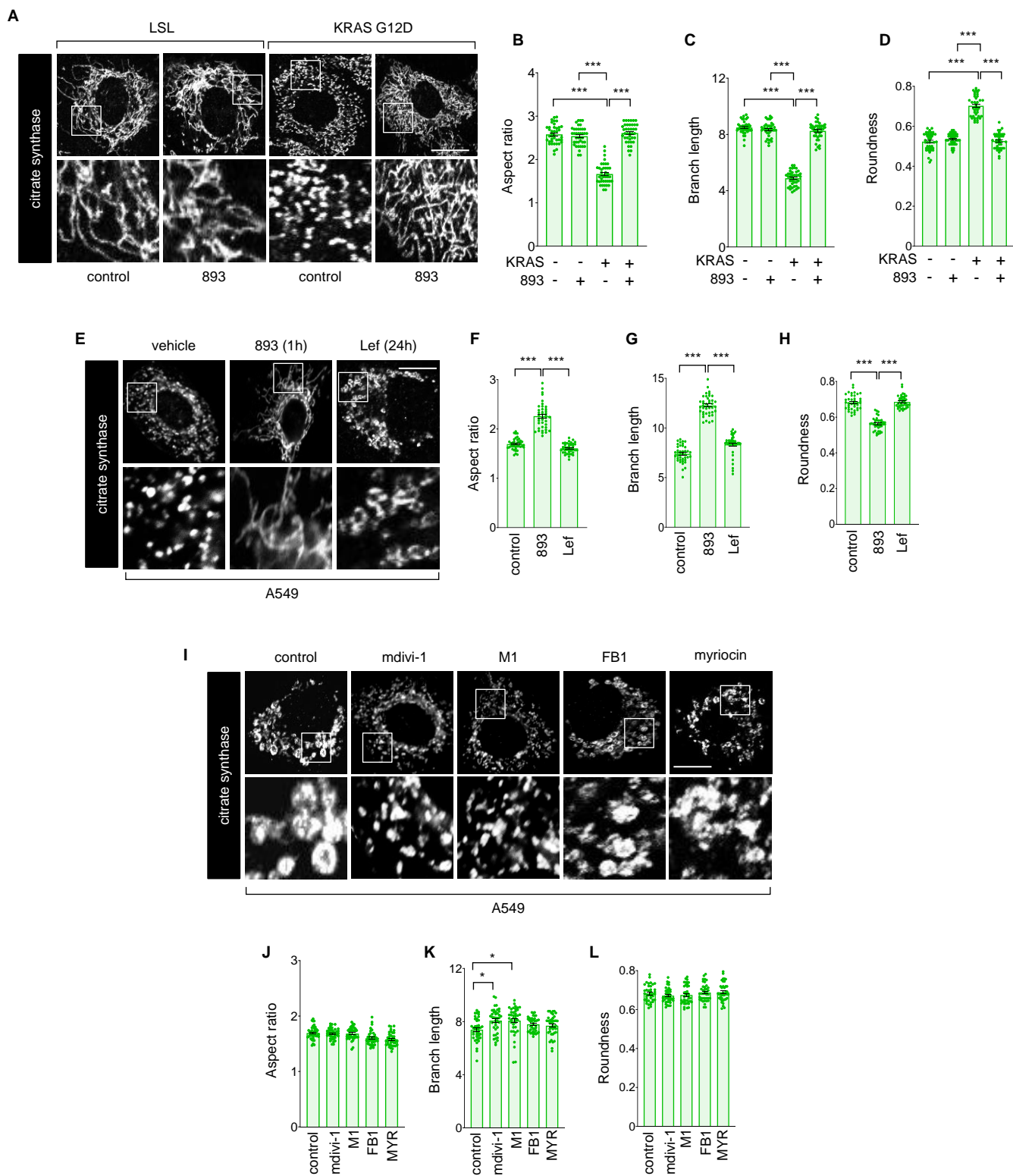


**APPENDIX**  
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**Figure S1: SH-BC-893 opposes KRAS-induced mitochondrial fission more effectively than other agents.** **A**, Control lox-stop-lox (LSL) or KRASG12D MEFs were treated with SH-BC-893 (5  $\mu$ M) for 3 h and stained for citrate synthase. **B-D**, Aspect ratio (**B**), branch length (**C**), or roundness (**D**) of mitochondria in the cells in (**A**). **E-H**, A549 cells were treated with vehicle (methanol) or 893 (5  $\mu$ M) for 1 h or leflunomide (50  $\mu$ M) for 24 h and mitochondrial morphology quantified as in (**A-D**). **I-L**, A549 cells were treated with vehicle (DMSO), mdivi-1 (50  $\mu$ M) for 24 h, M1 (5  $\mu$ M) for 24 h, fumonisin B1 (30  $\mu$ M) or myriocin (10  $\mu$ M) for 3 h and mitochondrial morphology quantified as in (**A-D**). In **B-D**, **F-H**, and **J-L**, 40 cells were evaluated from 2 biological replicates, mean  $\pm$  SD shown. Using a one-way ANOVA and Tukey's correction, \*,  $P < 0.05$ ; \*\*\*,  $P \leq 0.001$ ; unmarked, not significant,  $P > 0.05$ . Scale bars, 20  $\mu$ m.

EXACT P VALUES FOR ALL FIGURES

|                                       | P value | significance |
|---------------------------------------|---------|--------------|
| Figure 1B                             |         |              |
| BSA vs. PA                            | <0.0001 | ****         |
| BSA vs. PA:YM                         | <0.0001 | ****         |
| BSA vs. PA:NAV                        | <0.0001 | ****         |
| BSA vs. 893:PAL                       | 0.509   | ns           |
| PA vs. PA:YM                          | <0.0001 | ****         |
| PA vs. PA:NAV                         | <0.0001 | ****         |
| PA vs. 893:PAL                        | <0.0001 | ****         |
| PA:YM vs. PA:NAV                      | 0.003   | **           |
| PA:YM vs. 893:PAL                     | <0.0001 | ****         |
| PA:NAV vs. 893:PAL                    | 0.0002  | ***          |
| Figure 1C                             |         |              |
| BSA vs. PA                            | <0.0001 | ****         |
| BSA vs. PA:YM                         | <0.0001 | ****         |
| BSA vs. PA:NAV                        | <0.0001 | ****         |
| BSA vs. 893:PAL                       | 0.0157  | *            |
| PA vs. PA:YM                          | <0.0001 | ****         |
| PA vs. PA:NAV                         | <0.0001 | ****         |
| PA vs. 893:PAL                        | <0.0001 | ****         |
| PA:YM vs. PA:NAV                      | 0.9816  | ns           |
| PA:YM vs. 893:PAL                     | <0.0001 | ****         |
| PA:NAV vs. 893:PAL                    | <0.0001 | ****         |
| Figure 1D                             |         |              |
| BSA vs. PA                            | <0.0001 | ****         |
| BSA vs. PA:YM                         | <0.0001 | ****         |
| BSA vs. PA:NAV                        | <0.0001 | ****         |
| BSA vs. 893:PAL                       | 0.8167  | ns           |
| PA vs. PA:YM                          | <0.0001 | ****         |
| PA vs. PA:NAV                         | <0.0001 | ****         |
| PA vs. 893:PAL                        | <0.0001 | ****         |
| PA:YM vs. PA:NAV                      | >0.9999 | ns           |
| PA:YM vs. 893:PAL                     | 0.0004  | ***          |
| PA:NAV vs. 893:PAL                    | 0.0004  | ***          |
| Figure 1F                             |         |              |
| BSA vs. PA                            | <0.0001 | ****         |
| BSA vs. c16 cer                       | <0.0001 | ****         |
| BSA vs. 893:PA 1 h pre-treat          | 0.0026  | **           |
| BSA vs. 893:c16 cer 1 h pre-treat     | >0.9999 | ns           |
| PA vs. c16 cer                        | 0.5051  | ns           |
| PA vs. 893:PA 1 h pre-treat           | <0.0001 | ****         |
| PA vs. 893:c16 cer 1 h pre-treat      | <0.0001 | ****         |
| c16 cer vs. 893:PA 1 h pre-treat      | <0.0001 | ****         |
| c16 cer vs. 893:c16 cer 1 h pre-treat | <0.0001 | ****         |

|  |         |      |
|--|---------|------|
| 893:PA 1 h pre-treat vs. 893:c16 cer 1 h pre-treat | 0.0026  | **   |
| Figure 1G  |         |      |
| BSA vs. PA   | <0.0001 | **** |
| BSA vs. c16 cer                                    | <0.0001 | **** |
| BSA vs. 893:PA 1 h pre-treat                       | 0.0433  | *    |
| BSA vs. 893:c16 cer 1 h pre-treat                  | <0.0001 | **** |
| PA vs. c16 cer                                     | >0.9999 | ns   |
| PA vs. 893:PA 1 h pre-treat                        | <0.0001 | **** |
| PA vs. 893:c16 cer 1 h pre-treat                   | <0.0001 | **** |
| c16 cer vs. 893:PA 1 h pre-treat                   | <0.0001 | **** |
| c16 cer vs. 893:c16 cer 1 h pre-treat              | <0.0001 | **** |
| 893:PA 1 h pre-treat vs. 893:c16 cer 1 h pre-treat | <0.0001 | **** |
| Figure 1H  |         |      |
| BSA vs. PA   | <0.0001 | **** |
| BSA vs. c16 cer                                    | <0.0001 | **** |
| BSA vs. 893:PA 1 h pre-treat                       | 0.0073  | **   |
| BSA vs. 893:c16 cer 1 h pre-treat                  | 0.8194  | ns   |
| PA vs. c16 cer                                     | 0.5496  | ns   |
| PA vs. 893:PA 1 h pre-treat                        | <0.0001 | **** |
| PA vs. 893:c16 cer 1 h pre-treat                   | <0.0001 | **** |
| c16 cer vs. 893:PA 1 h pre-treat                   | <0.0001 | **** |
| c16 cer vs. 893:c16 cer 1 h pre-treat              | <0.0001 | **** |
| 893:PA 1 h pre-treat vs. 893:c16 cer 1 h pre-treat | 0.1424  | ns   |
| Figure 1I  |         |      |
| Vehicle  | 0.0009  | ***  |
| 893  | 0.0018  | **   |
| Myriocin   | 0.1443  | ns   |
| Fumonisin B1                                       | 0.4298  | ns   |
| Figure 1K  |         |      |
| BSA vs. PA   | <0.0001 | **** |
| BSA vs. 893  | 0.9989  | ns   |
| BSA vs. 893PA                                      | 0.5568  | ns   |
| PA vs. 893   | <0.0001 | **** |
| PA vs. 893PA                                       | <0.0001 | **** |
| 893 vs. 893PA                                      | 0.8708  | ns   |
| Figure 1M  |         |      |
| BSA vs. BSA+893                                    | 0.3989  | ns   |
| BSA vs. PA   | 0.7932  | ns   |
| BSA vs. PA+893                                     | 0.7267  | ns   |
| BSA+893 vs. PA                                     | 0.8779  | ns   |
| BSA+893 vs. PA+893                                 | 0.0994  | ns   |
| PA vs. PA+893                                      | 0.2729  | ns   |
| Figure 1O  |         |      |
| BSA vs. PAL  | <0.0001 | **** |
| BSA vs. PAL VEC 893                                | 0.731   | ns   |

|                                  |         |      |
|----------------------------------|---------|------|
| BSA vs. PAL TRPML 893            | <0.0001 | **** |
| BSA vs. PAL GRP1DD 893           | <0.0001 | **** |
| PAL vs. PAL VEC 893              | <0.0001 | **** |
| PAL vs. PAL TRPML 893            | 0.0017  | **   |
| PAL vs. PAL GRP1DD 893           | >0.9999 | ns   |
| PAL VEC 893 vs. PAL TRPML 893    | <0.0001 | **** |
| PAL VEC 893 vs. PAL GRP1DD 893   | <0.0001 | **** |
| PAL TRPML 893 vs. PAL GRP1DD 893 | 0.0231  | *    |
| Figure 1P                        |         |      |
| BSA vs. PAL                      | <0.0001 | **** |
| BSA vs. PAL VEC 893              | 0.0869  | ns   |
| BSA vs. PAL TRPML 893            | <0.0001 | **** |
| BSA vs. PAL GRP1DD 893           | <0.0001 | **** |
| PAL vs. PAL VEC 893              | <0.0001 | **** |
| PAL vs. PAL TRPML 893            | 0.0297  | *    |
| PAL vs. PAL GRP1DD 893           | 0.0015  | **   |
| PAL VEC 893 vs. PAL TRPML 893    | <0.0001 | **** |
| PAL VEC 893 vs. PAL GRP1DD 893   | <0.0001 | **** |
| PAL TRPML 893 vs. PAL GRP1DD 893 | 0.8915  | ns   |
| Figure 1Q                        |         |      |
| BSA vs. PAL                      | <0.0001 | **** |
| BSA vs. PAL VEC 893              | 0.9964  | ns   |
| BSA vs. PAL TRPML 893            | <0.0001 | **** |
| BSA vs. PAL GRP1DD 893           | <0.0001 | **** |
| PAL vs. PAL VEC 893              | <0.0001 | **** |
| PAL vs. PAL TRPML 893            | 0.0939  | ns   |
| PAL vs. PAL GRP1DD 893           | 0.3264  | ns   |
| PAL VEC 893 vs. PAL TRPML 893    | <0.0001 | **** |
| PAL VEC 893 vs. PAL GRP1DD 893   | <0.0001 | **** |
| PAL TRPML 893 vs. PAL GRP1DD 893 | 0.9727  | ns   |
| Figure 2B                        |         |      |
| control vs. PAL                  | <0.0001 | **** |
| control vs. PAL:893              | 0.001   | **   |
| PAL vs. PAL:893                  | <0.0001 | **** |
| Figure 2D                        |         |      |
| control vs. PAL                  | <0.0001 | **** |
| control vs. PAL:893              | 0.9019  | ns   |
| PAL vs. PAL:893                  | <0.0001 | **** |
| Figure 2E                        |         |      |
| CHOP                             |         |      |
| bsa vs. palmitate                | <0.0001 | **** |
| bsa vs. bsa 893                  | 0.9978  | ns   |
| bsa vs. pal 893                  | 0.9269  | ns   |
| palmitate vs. bsa 893            | <0.0001 | **** |
| palmitate vs. pal 893            | <0.0001 | **** |
| bsa 893 vs. pal 893              | 0.972   | ns   |
| XBP1s                            |         |      |
| bsa vs. palmitate                | <0.0001 | **** |
| bsa vs. bsa 893                  | 0.9932  | ns   |
| bsa vs. pal 893                  | 0.9125  | ns   |
| palmitate vs. bsa 893            | <0.0001 | **** |

|                                  |         |      |
|----------------------------------|---------|------|
| palmitate vs. pal 893            | <0.0001 | **** |
| bsa 893 vs. pal 893              | 0.9787  | ns   |
| ATF6                             |         |      |
| bsa vs. palmitate                | 0.0002  | ***  |
| bsa vs. bsa 893                  | 0.0964  | ns   |
| bsa vs. pal 893                  | 0.0103  | *    |
| palmitate vs. bsa 893            | <0.0001 | **** |
| palmitate vs. pal 893            | <0.0001 | **** |
| bsa 893 vs. pal 893              | 0.4171  | ns   |
| GRP78                            |         |      |
| bsa vs. palmitate                | 0.0022  | **   |
| bsa vs. bsa 893                  | 0.7849  | ns   |
| bsa vs. pal 893                  | 0.3266  | ns   |
| palmitate vs. bsa 893            | 0.0008  | ***  |
| palmitate vs. pal 893            | 0.0003  | ***  |
| bsa 893 vs. pal 893              | 0.8097  | ns   |
| Figure 3A                        |         |      |
| SD veh vs. SD 893                | 0.617   | ns   |
| SD veh vs. HFD veh               | <0.0001 | **** |
| SD veh vs. HFD 893               | <0.0001 | **** |
| SD 893 vs. HFD veh               | <0.0001 | **** |
| SD 893 vs. HFD 893               | <0.0001 | **** |
| HFD veh vs. HFD 893              | 0.9925  | ns   |
| Figure 3C                        |         |      |
| Vehicle:SD vs. 893:SD            | 0.2201  | ns   |
| Vehicle:SD vs. Vehicle:HFD       | <0.0001 | **** |
| Vehicle:SD vs. 893:HFD           | 0.1839  | ns   |
| 893:SD vs. Vehicle:HFD           | <0.0001 | **** |
| 893:SD vs. 893:HFD               | 0.9997  | ns   |
| Vehicle:HFD vs. 893:HFD          | <0.0001 | **** |
| Figure 3D                        |         |      |
| Vehicle:SD vs. 893:SD            | 0.7215  | ns   |
| Vehicle:SD vs. Vehicle:HFD       | <0.0001 | **** |
| Vehicle:SD vs. 893:HFD           | 0.421   | ns   |
| 893:SD vs. Vehicle:HFD           | <0.0001 | **** |
| 893:SD vs. 893:HFD               | 0.0522  | ns   |
| Vehicle:HFD vs. 893:HFD          | <0.0001 | **** |
| Figure 3E                        |         |      |
| Untreated SD vs. 120mpk 893 SD   | 0.9922  | ns   |
| Untreated SD vs. Untreated HFD   | <0.0001 | **** |
| Untreated SD vs. 120mpk 893 HFD  | <0.0001 | **** |
| 120mpk 893 SD vs. Untreated HFD  | <0.0001 | **** |
| 120mpk 893 SD vs. 120mpk 893 HFD | <0.0001 | **** |
| Untreated HFD vs. 120mpk 893 HFD | 0.9986  | ns   |
| Figure 3H                        |         |      |
| Vehicle:SD vs. 893:SD            | 0.0122  | *    |
| Vehicle:SD vs. Vehicle:HFD       | <0.0001 | **** |
| Vehicle:SD vs. 893:HFD           | <0.0001 | **** |
| 893:SD vs. Vehicle:HFD           | <0.0001 | **** |
| 893:SD vs. 893:HFD               | 0.0065  | **   |
| Vehicle:HFD vs. 893:HFD          | <0.0001 | **** |
| Figure 3I                        |         |      |
| Vehicle:SD vs. 893:SD            | 0.0065  | **   |
| Vehicle:SD vs. Vehicle:HFD       | <0.0001 | **** |
| Vehicle:SD vs. 893:HFD           | <0.0001 | **** |
| 893:SD vs. Vehicle:HFD           | <0.0001 | **** |
| 893:SD vs. 893:HFD               | 0.2952  | ns   |
| Vehicle:HFD vs. 893:HFD          | <0.0001 | **** |
| Figure 3K                        |         |      |
| Vehicle:SD vs. 893:SD            | 0.6348  | ns   |
| Vehicle:SD vs. Vehicle:HFD       | <0.0001 | **** |
| Vehicle:SD vs. 893:HFD           | 0.0033  | **   |

|  |   |  |
|--|---|--|
| 893:SD vs. Vehicle:HFD<br>893:SD vs. 893:HFD<br>Vehicle:HFD vs. 893:HFD  | <0.0001<br>0.0855<br><0.0001                                  | ****<br>ns<br>****                         |
| Figure 3L  |   |  |
| Vehicle:SD vs. 893:SD<br>Vehicle:SD vs. Vehicle:HFD<br>Vehicle:SD vs. 893:HFD<br>893:SD vs. Vehicle:HFD<br>893:SD vs. 893:HFD<br>Vehicle:HFD vs. 893:HFD   | 0.144<br><0.0001<br>0.9995<br><0.0001<br>0.1149<br><0.0001    | ns<br>****<br>ns<br>****<br>ns<br>****     |
| Figure 4A  |   |  |
| SD veh vs. SD 893<br>SD veh vs. HFD veh<br>SD veh vs. HFD 893<br>SD 893 vs. HFD veh<br>SD 893 vs. HFD 893<br>HFD veh vs. HFD 893   | 0.9815<br><0.0001<br><0.0001<br><0.0001<br><0.0001<br>>0.9999 | ns<br>****<br>****<br>****<br>****<br>ns   |
| Figure 4C  |   |  |
| VEH:SD vs. 893:SD<br>VEH:SD vs. VEH:HFD<br>VEH:SD vs. 893:HFD<br>893:SD vs. VEH:HFD<br>893:SD vs. 893:HFD<br>VEH:HFD vs. 893:HFD   | <0.0001<br><0.0001<br><0.0001<br><0.0001<br>0.9205<br><0.0001 | ****<br>****<br>****<br>****<br>ns<br>**** |
| Figure 4D  |   |  |
| Untreated SD vs. 120mpk 893 SD<br>Untreated SD vs. Untreated HFD<br>Untreated SD vs. 120mpk 893 HFD<br>120mpk 893 SD vs. Untreated HFD<br>120mpk 893 SD vs. 120mpk 893 HFD<br>Untreated HFD vs. 120mpk 893 HFD | 0.974<br><0.0001<br><0.0001<br><0.0001<br><0.0001<br>>0.9999  | ns<br>****<br>****<br>****<br>****<br>ns   |
| Figure 4F  |   |  |
| VEH:SD vs. 893:SD<br>VEH:SD vs. VEH:HFD<br>VEH:SD vs. 893:HFD<br>893:SD vs. VEH:HFD<br>893:SD vs. 893:HFD<br>VEH:HFD vs. 893:HFD   | 0.005<br><0.0001<br><0.0001<br><0.0001<br>0.0013<br><0.0001   | **<br>****<br>****<br>****<br>**<br>****   |
| Figure 4G  |   |  |
| VEH:SD vs. 893:SD<br>VEH:SD vs. VEH:HFD<br>VEH:SD vs. 893:HFD<br>893:SD vs. VEH:HFD<br>893:SD vs. 893:HFD<br>VEH:HFD vs. 893:HFD   | 0.9057<br><0.0001<br><0.0001<br><0.0001<br><0.0001<br>0.8676  | ns<br>****<br>****<br>****<br>****<br>ns   |
| Figure 4I  |   |  |
| VEH:SD vs. 893:SD<br>VEH:SD vs. VEH:HFD<br>VEH:SD vs. 893:HFD<br>893:SD vs. VEH:HFD<br>893:SD vs. 893:HFD<br>VEH:HFD vs. 893:HFD   | 0.9998<br><0.0001<br><0.0001<br><0.0001<br><0.0001<br><0.0001 | ns<br>****<br>****<br>****<br>****<br>**** |
| Figure 4J  |   |  |
| VEH:SD vs. 893:SD<br>VEH:SD vs. VEH:HFD<br>VEH:SD vs. 893:HFD<br>893:SD vs. VEH:HFD<br>893:SD vs. 893:HFD<br>VEH:HFD vs. 893:HFD   | 0.9342<br><0.0001<br><0.0001<br><0.0001<br><0.0001<br>0.7519  | ns<br>****<br>****<br>****<br>****<br>ns   |
| Figure 4K  |   |  |
| CHOP<br>XBP1s  | 0.0401<br>0.0804  | *<br>ns                                    |



|  |  |   |
|--|--|---|
| ATF6<br>GRP78  | 0.057<br>0.0494  | ns<br>*                                   |
| Figure 5A  |  |   |
| SD vs. HFD vehicle<br>SD vs. HFD 893<br>SD vs. HFD pair-fed<br>HFD vehicle vs. HFD 893<br>HFD vehicle vs. HFD pair-fed<br>HFD 893 vs. HFD pair-fed | <0.0001<br><0.0001<br><0.0001<br>0.0006<br>0.0554<br><0.0001 | ****<br>****<br>****<br>***<br>ns<br>**** |
| Figure 5B  |  |   |
| SD vs. HFD vehicle<br>SD vs. HFD 893<br>SD vs. HFD pair-fed<br>HFD vehicle vs. HFD 893<br>HFD vehicle vs. HFD pair-fed<br>HFD 893 vs. HFD pair-fed | 0.0101<br>0.8744<br>0.0037<br>0.019<br>0.6772<br>0.0112      | *<br>ns<br>**<br>*<br>ns<br>*             |
| Figure 5C  |  |   |
| SD vs. HFD vehicle<br>SD vs. HFD 893<br>SD vs. HFD pair-fed<br>HFD vehicle vs. HFD 893<br>HFD vehicle vs. HFD pair-fed<br>HFD 893 vs. HFD pair-fed | 0.002<br>0.0431<br>0.0017<br>0.0029<br>0.973<br>0.0035       | **<br>*<br>**<br>**<br>ns<br>**           |
| Figure 5D  |  |   |
| Rx 1<br>Rx 3<br>Rx 6<br>Rx 9   | 0.0024<br>0.0835<br>0.1403<br>0.3509                         | **<br>ns<br>ns<br>ns                      |
| Figure 5E  |  |   |
| Rx 1<br>Rx 3<br>Rx 6<br>Rx 9   | 0.0016<br>0.0006<br>0.0006<br>0.0008                         | **<br>***<br>***<br>***                   |
| Figure 5F  |  |   |
| Rx 1<br>Rx 3<br>Rx 6<br>Rx 9   | 0.0001<br>0.1042<br>0.0335<br>0.0065                         | ***<br>ns<br>*<br>**                      |
| Figure 5G  | 0.0186   | *   |
| Figure 5H  | 0.0043   | **  |
| Figure 5J  |  |   |
| 0<br>4<br>8<br>10<br>16  | 0.0164<br>0.0011<br>0.0029<br>0.0025<br>0.0001               | *<br>***<br>**<br>**<br>***               |
| Figure 5K  |  |   |
| 0<br>4<br>8<br>10<br>16  | 0.1235<br>0.0000<br>0.0033<br>0.0136<br>0.0024               | ns<br>***<br>**<br>*<br>**                |
| Figure 5L  |  |   |
| 0<br>4<br>8<br>10<br>16  | 0.1898<br>0.0004<br>0.0006<br>0.0019<br>0.0001               | ns<br>***<br>***<br>**<br>***             |
| Figure 6B  |  |   |
| 1<br>2<br>3  | 0.0057<br>0.2985<br>0.0174                                   | **<br>ns<br>*                             |

|  |         |      |
|--|---------|------|
| 4                                      | 0.5965  | ns   |
| Figure 6D                              |         |      |
| 1                                      | 0.0071  | **   |
| 2                                      | 0.6322  | ns   |
| 3                                      | 0.0159  | *    |
| 4                                      | 0.6017  | ns   |
| Figure 6E                              |         |      |
| vehicle vs. 893                        | <0.0001 | **** |
| vehicle vs. pair-fed                   | 0.0003  | ***  |
| 893 vs. pair-fed                       | 0.8575  | ns   |
| Figure 6F                              |         |      |
| Day 49                                 |         |      |
| SD:VEH vs. hfd:veh                     | 0.0003  | ***  |
| SD:VEH vs. hfd:60mpk 893               | 0.0049  | **   |
| SD:VEH vs. hfd:120 mpk 893             | 0.0045  | **   |
| hfd:veh vs. hfd:60mpk 893              | 0.8421  | ns   |
| hfd:veh vs. hfd:120 mpk 893            | 0.7943  | ns   |
| hfd:60mpk 893 vs. hfd:120 mpk 893      | 0.9999  | ns   |
| Day 53                                 |         |      |
| SD:VEH vs. hfd:veh                     | 0.0002  | ***  |
| SD:VEH vs. hfd:60mpk 893               | 0.049   | *    |
| SD:VEH vs. hfd:120 mpk 893             | 0.0757  | ns   |
| hfd:veh vs. hfd:60mpk 893              | 0.2365  | ns   |
| hfd:veh vs. hfd:120 mpk 893            | 0.1307  | ns   |
| hfd:60mpk 893 vs. hfd:120 mpk 893      | 0.9936  | ns   |
| Day 60                                 |         |      |
| SD:VEH vs. hfd:veh                     | 0.0002  | ***  |
| SD:VEH vs. hfd:60mpk 893               | 0.1145  | ns   |
| SD:VEH vs. hfd:120 mpk 893             | 0.7592  | ns   |
| hfd:veh vs. hfd:60mpk 893              | 0.1227  | ns   |
| hfd:veh vs. hfd:120 mpk 893            | 0.0036  | **   |
| hfd:60mpk 893 vs. hfd:120 mpk 893      | 0.5354  | ns   |
| Day 67                                 |         |      |
| SD:VEH vs. hfd:veh                     | 0.0001  | ***  |
| SD:VEH vs. hfd:60mpk 893               | 0.1875  | ns   |
| SD:VEH vs. hfd:120 mpk 893             | 0.9769  | ns   |
| hfd:veh vs. hfd:60mpk 893              | 0.0435  | *    |
| hfd:veh vs. hfd:120 mpk 893            | 0.0004  | ***  |
| hfd:60mpk 893 vs. hfd:120 mpk 893      | 0.3593  | ns   |
| Day 73                                 |         |      |
| SD:VEH vs. hfd:veh                     | 0.0054  | **   |
| SD:VEH vs. hfd:60mpk 893               | 0.1853  | ns   |
| SD:VEH vs. hfd:120 mpk 893             | >0.9999 | ns   |
| hfd:veh vs. hfd:60mpk 893              | 0.2179  | ns   |
| hfd:veh vs. hfd:120 mpk 893            | 0.0064  | **   |
| hfd:60mpk 893 vs. hfd:120 mpk 893      | 0.25    | ns   |
| Figure 6G                              |         |      |
| SD:VEH vs. HFD:VEH                     | 0.5691  | ns   |
| SD:VEH vs. HFD:60 MPK 893              | 0.0003  | ***  |
| SD:VEH vs. HFD:120 MPK 893             | <0.0001 | **** |
| HFD:VEH vs. HFD:60 MPK 893             | <0.0001 | **** |
| HFD:VEH vs. HFD:120 MPK 893            | <0.0001 | **** |
| HFD:60 MPK 893 vs. HFD:120 MPK 893     | <0.0001 | **** |
| Figure 6H                              |         |      |
| Standard Diet vs. HFD + Vehicle        | <0.0001 | **** |
| Standard Diet vs. HFD + 60 mpk 893     | 0.1685  | ns   |
| Standard Diet vs. HFD + 120 mpk 893    | 0.9016  | ns   |
| HFD + Vehicle vs. HFD + 60 mpk 893     | 0.0019  | **   |
| HFD + Vehicle vs. HFD + 120 mpk 893    | <0.0001 | **** |
| HFD + 60 mpk 893 vs. HFD + 120 mpk 893 | 0.4801  | ns   |
| Figure 6I                              |         |      |
| SD:VEH vs. HFD:VEH                     | 0.3922  | ns   |
| SD:VEH vs. HFD:60 MPK 893              | 0.9851  | ns   |

|   |         |      |
|---|---------|------|
| SD:VEH vs. HFD:120 MPK 893                          | <0.0001 | **** |
| HFD:VEH vs. HFD:60 MPK 893                          | 0.3448  | ns   |
| HFD:VEH vs. HFD:120 MPK 893                         | 0.0001  | ***  |
| HFD:60 MPK 893 vs. HFD:120 MPK 893                  | 0.0062  | **   |
| Figure 6L   | 0.9521  | ns   |
| Figure 6J   |         |      |
| Standard Diet vs. HFD + Vehicle                     | 0.6327  | ns   |
| Standard Diet vs. HFD + 60 mpk 893                  | 0.8207  | ns   |
| Standard Diet vs. HFD + 120 mpk 893                 | 0.8397  | ns   |
| HFD + Vehicle vs. HFD + 60 mpk 893                  | 0.9908  | ns   |
| HFD + Vehicle vs. HFD + 120 mpk 893                 | 0.1975  | ns   |
| HFD + 60 mpk 893 vs. HFD + 120 mpk 893              | 0.3506  | ns   |
| Figure 6K   |         |      |
| SD:VEH vs. HFD:VEH                                  | 0.7292  | ns   |
| SD:VEH vs. HFD:60 MPK 893                           | <0.0001 | **** |
| SD:VEH vs. HFD:120 MPK 893                          | <0.0001 | **** |
| HFD:VEH vs. HFD:60 MPK 893                          | 0.0006  | ***  |
| HFD:VEH vs. HFD:120 MPK 893                         | 0.0001  | ***  |
| HFD:60 MPK 893 vs. HFD:120 MPK 893                  | 0.9671  | ns   |
| Figure 6M   |         |      |
| SD vs. veh hfd                                      | 0.6012  | ns   |
| SD vs. 893 hfd                                      | <0.0001 | **** |
| SD vs. wheel hfd                                    | <0.0001 | **** |
| SD vs. wheel 893 hfd                                | <0.0001 | **** |
| veh hfd vs. 893 hfd                                 | <0.0001 | **** |
| veh hfd vs. wheel hfd                               | <0.0001 | **** |
| veh hfd vs. wheel 893 hfd                           | <0.0001 | **** |
| 893 hfd vs. wheel hfd                               | 0.008   | **   |
| 893 hfd vs. wheel 893 hfd                           | <0.0001 | **** |
| wheel hfd vs. wheel 893 hfd                         | <0.0001 | **** |
| Figure 6N   |         |      |
| SD vs. HFD + Vehicle                                | <0.0001 | **** |
| SD vs. HFD + 120 mpk 893                            | 0.958   | ns   |
| SD vs. HFD + Vehicle + Wheel                        | 0.1533  | ns   |
| SD vs. HFD + 120 mpk 893 + Wheel                    | 0.9331  | ns   |
| HFD + Vehicle vs. HFD + 120 mpk 893                 | <0.0001 | **** |
| HFD + Vehicle vs. HFD + Vehicle + Wheel             | 0.0071  | **   |
| HFD + Vehicle vs. HFD + 120 mpk 893 + Wheel         | <0.0001 | **** |
| HFD + 120 mpk 893 vs. HFD + Vehicle + Wheel         | 0.4489  | ns   |
| HFD + 120 mpk 893 vs. HFD + 120 mpk 893 + Wheel     | 0.6427  | ns   |
| HFD + Vehicle + Wheel vs. HFD + 120 mpk 893 + Wheel | 0.0562  | ns   |
| Figure 6O   |         |      |
| SD vs. SD 893                                       | 0.0076  | **   |
| SD vs. HFD VEH                                      | <0.0001 | **** |
| SD vs. HFD 893                                      | 0.2512  | ns   |
| SD 893 vs. HFD VEH                                  | <0.0001 | **** |
| SD 893 vs. HFD 893                                  | <0.0001 | **** |
| HFD VEH vs. HFD 893                                 | <0.0001 | **** |
| Figure 6P   |         |      |
| SD vs. SD 893                                       | 0.0075  | **   |
| SD vs. HFD VEH                                      | >0.9999 | ns   |
| SD vs. HFD 893                                      | <0.0001 | **** |
| SD 893 vs. HFD VEH                                  | 0.0075  | **   |
| SD 893 vs. HFD 893                                  | 0.0641  | ns   |
| HFD VEH vs. HFD 893                                 | <0.0001 | **** |
| Figure 6R   |         |      |
| SD vs. SD 893                                       | 0.0248  | *    |
| SD vs. HFD VEH                                      | 0.9981  | ns   |
| SD vs. HFD 893                                      | <0.0001 | **** |
| SD 893 vs. HFD VEH                                  | 0.0162  | *    |
| SD 893 vs. HFD 893                                  | <0.0001 | **** |
| HFD VEH vs. HFD 893                                 | <0.0001 | **** |
| Figure 7C   |         |      |

|  |   |                             |
|--|---|-----------------------------|
| d17:1/22:0<br>sd vs. hfd<br>sd vs. hfd 893<br>hfd vs. hfd 893  | 0.0628<br>0.0324<br>0.9065                      | ns<br>*<br>ns               |
| d18:1/16:0<br>sd vs. hfd<br>sd vs. hfd 893<br>hfd vs. hfd 893  | 0.0635<br>0.6841<br>0.017                       | ns<br>ns<br>*               |
| d18:1/18:0<br>sd vs. hfd<br>sd vs. hfd 893<br>hfd vs. hfd 893  | 0.5271<br>0.7527<br>0.2089                      | ns<br>ns<br>ns              |
| d18:1/20:0<br>sd vs. hfd<br>sd vs. hfd 893<br>hfd vs. hfd 893  | 0.0033<br>0.4125<br>0.024                       | **<br>ns<br>*               |
| d18:1/22:0<br>sd vs. hfd<br>sd vs. hfd 893<br>hfd vs. hfd 893  | 0.1027<br>0.2328<br>0.8464                      | ns<br>ns<br>ns              |
| d18:1/22:1<br>sd vs. hfd<br>sd vs. hfd 893<br>hfd vs. hfd 893  | 0.4812<br>0.4557<br>0.0848                      | ns<br>ns<br>ns              |
| d18:1/23:0<br>sd vs. hfd<br>sd vs. hfd 893<br>hfd vs. hfd 893  | 0.3986<br>0.513<br>0.974                        | ns<br>ns<br>ns              |
| d18:1/24:0<br>sd vs. hfd<br>sd vs. hfd 893<br>hfd vs. hfd 893  | 0.7884<br>0.9571<br>0.923                       | ns<br>ns<br>ns              |
| d18:1/24:1<br>sd vs. hfd<br>sd vs. hfd 893<br>hfd vs. hfd 893  | 0.7359<br>0.888<br>0.9544                       | ns<br>ns<br>ns              |
| d18:2/18:0<br>sd vs. hfd<br>sd vs. hfd 893<br>hfd vs. hfd 893  | 0.9577<br>0.7692<br>0.6061                      | ns<br>ns<br>ns              |
| d18:2/22:0<br>sd vs. hfd<br>sd vs. hfd 893<br>hfd vs. hfd 893  | 0.098<br>0.6517<br>0.3561                       | ns<br>ns<br>ns              |
| d18:2/24:1<br>sd vs. hfd<br>sd vs. hfd 893<br>hfd vs. hfd 893  | 0.2949<br>0.9964<br>0.3278                      | ns<br>ns<br>ns              |
| Figure 7D  |   |                             |
| SD vs. HFD + vehicle<br>SD vs. HFD + 893<br>HFD + vehicle vs. HFD + 893  | 0.0863<br>0.9436<br>0.0521                      | ns<br>ns<br>ns              |
| Figure 7E  |   |                             |
| SD vs. HFD Vehicle<br>SD vs. HFD 60mpk 893<br>SD vs. HFD 120 mpk 893<br>HFD Vehicle h vs. HFD 60mpk 893<br>HFD Vehicle vs. HFD 120 mpk 893   | 0.0006<br>0.0757<br>>0.9999<br>0.2574<br>0.0018 | ***<br>ns<br>ns<br>ns<br>** |
| Figure 7G  |   |                             |
| SD vs. HFD + Vehicle<br>SD vs. HFD + 60 mg/kg 893<br>SD vs. HFD + 120 mg/kg 893 - Trough<br>HFD + Vehicle vs. HFD + 60 mg/kg 893<br>HFD + Vehicle vs. HFD + 120 mg/kg 893 - Trough | 0.0055<br>0.9882<br>0.9941<br>0.0244<br>0.0213  | **<br>ns<br>ns<br>*<br>*    |

|   |         |      |
|---|---------|------|
| HFD + 60 mg/kg 893 vs. HFD + 120 mg/kg 893 - Trough | >0.9999 | ns   |
| Figure 7H   |         |      |
| SD vs. HFD Rx1 VEH                                  | 0.0861  | ns   |
| SD vs. HFD Rx1 893                                  | 0.9849  | ns   |
| SD vs. HFD Rx9 VEH                                  | 0.0007  | ***  |
| SD vs. HFD Rx9 893                                  | 0.1497  | ns   |
| HFD Rx1 VEH vs. HFD Rx1 893                         | 0.2374  | ns   |
| HFD Rx1 VEH vs. HFD Rx9 VEH                         | 0.3787  | ns   |
| HFD Rx1 VEH vs. HFD Rx9 893                         | 0.0002  | ***  |
| HFD Rx1 893 vs. HFD Rx9 VEH                         | 0.0033  | **   |
| HFD Rx1 893 vs. HFD Rx9 893                         | 0.0492  | *    |
| HFD Rx9 VEH vs. HFD Rx9 893                         | <0.0001 | **** |
| Figure 7I   |         |      |
| sd vs. HFD vehicle                                  | 0.3388  | ns   |
| sd vs. HFD 893                                      | 0.0029  | **   |
| sd vs. HFD pair-fed                                 | 0.0021  | **   |
| HFD vehicle vs. HFD 893                             | 0.0337  | *    |
| HFD vehicle vs. HFD pair-fed                        | 0.0299  | *    |
| HFD 893 vs. HFD pair-fed                            | 0.9994  | ns   |
| Figure EV2B   |         |      |
| ETOH vs. C16-CER                                    | <0.0001 | **** |
| ETOH vs. ETOH+Mdivi1+M1 1 h                         | 0.3836  | ns   |
| ETOH vs. CER:MdiviM1 1 h                            | <0.0001 | **** |
| ETOH vs. ETOH:Mdivi1+M1 24 h                        | >0.9999 | ns   |
| ETOH vs. CER:Mdivi1+M1 24 h                         | <0.0001 | **** |
| C16-CER vs. ETOH+Mdivi1+M1 1 h                      | <0.0001 | **** |
| C16-CER vs. CER:MdiviM1 1 h                         | 0.9072  | ns   |
| C16-CER vs. ETOH:Mdivi1+M1 24 h                     | <0.0001 | **** |
| C16-CER vs. CER:Mdivi1+M1 24 h                      | >0.9999 | ns   |
| ETOH+Mdivi1+M1 1 h vs. CER:MdiviM1 1 h              | <0.0001 | **** |
| ETOH+Mdivi1+M1 1 h vs. ETOH:Mdivi1+M1 24 h          | 0.2996  | ns   |
| ETOH+Mdivi1+M1 1 h vs. CER:Mdivi1+M1 24 h           | <0.0001 | **** |
| CER:MdiviM1 1 h vs. ETOH:Mdivi1+M1 24 h             | <0.0001 | **** |
| CER:MdiviM1 1 h vs. CER:Mdivi1+M1 24 h              | 0.9113  | ns   |
| ETOH:Mdivi1+M1 24 h vs. CER:Mdivi1+M1 24 h          | <0.0001 | **** |
| Figure EV2C   |         |      |
| ETOH vs. C16-CER                                    | <0.0001 | **** |
| ETOH vs. ETOH+Mdivi1+M1 1 h                         | 0.1119  | ns   |
| ETOH vs. CER:MdiviM1 1 h                            | <0.0001 | **** |
| ETOH vs. ETOH:Mdivi1+M1 24 h                        | 0.4579  | ns   |
| ETOH vs. CER:Mdivi1+M1 24 h                         | <0.0001 | **** |
| C16-CER vs. ETOH+Mdivi1+M1 1 h                      | <0.0001 | **** |
| C16-CER vs. CER:MdiviM1 1 h                         | 0.0902  | ns   |
| C16-CER vs. ETOH:Mdivi1+M1 24 h                     | <0.0001 | **** |
| C16-CER vs. CER:Mdivi1+M1 24 h                      | 0.0062  | **   |
| ETOH+Mdivi1+M1 1 h vs. CER:MdiviM1 1 h              | <0.0001 | **** |
| ETOH+Mdivi1+M1 1 h vs. ETOH:Mdivi1+M1 24 h          | 0.9946  | ns   |
| ETOH+Mdivi1+M1 1 h vs. CER:Mdivi1+M1 24 h           | <0.0001 | **** |
| CER:MdiviM1 1 h vs. ETOH:Mdivi1+M1 24 h             | <0.0001 | **** |
| CER:MdiviM1 1 h vs. CER:Mdivi1+M1 24 h              | 0.8549  | ns   |
| ETOH:Mdivi1+M1 24 h vs. CER:Mdivi1+M1 24 h          | <0.0001 | **** |
| Figure EV2D   |         |      |
| ETOH vs. C16-CER                                    | <0.0001 | **** |
| ETOH vs. ETOH+Mdivi1+M1 1 h                         | 0.0898  | ns   |
| ETOH vs. CER:MdiviM1 1 h                            | <0.0001 | **** |
| ETOH vs. ETOH:Mdivi1+M1 24 h                        | 0.0116  | *    |
| ETOH vs. CER:Mdivi1+M1 24 h                         | <0.0001 | **** |
| C16-CER vs. ETOH+Mdivi1+M1 1 h                      | <0.0001 | **** |
| C16-CER vs. CER:MdiviM1 1 h                         | >0.9999 | ns   |
| C16-CER vs. ETOH:Mdivi1+M1 24 h                     | <0.0001 | **** |
| C16-CER vs. CER:Mdivi1+M1 24 h                      | 0.9696  | ns   |
| ETOH+Mdivi1+M1 1 h vs. CER:MdiviM1 1 h              | <0.0001 | **** |
| ETOH+Mdivi1+M1 1 h vs. ETOH:Mdivi1+M1 24 h          | <0.0001 | **** |
| ETOH+Mdivi1+M1 1 h vs. CER:Mdivi1+M1 24 h           | <0.0001 | **** |

|   |         |      |
|---|---------|------|
| CER:MdiviM1 1 h vs. ETOH:Mdivi1+M1 24 h       | <0.0001 | **** |
| CER:MdiviM1 1 h vs. CER:Mdivi1+M1 24 h        | 0.9935  | ns   |
| ETOH:Mdivi1+M1 24 h vs. CER:Mdivi1+M1 24 h    | <0.0001 | **** |
| Figure EV2F                                   |         |      |
| ETOH vs. C16CER                               | <0.0001 | **** |
| ETOH vs. ETOH:Lef 1 h                         | 0.5292  | ns   |
| ETOH vs. CER:LEF 1 H                          | <0.0001 | **** |
| ETOH vs. ETOH:Lef 24 h                        | 0.9941  | ns   |
| ETOH vs. CER:Lef 24 H                         | 0.1068  | ns   |
| C16CER vs. ETOH:Lef 1 h                       | <0.0001 | **** |
| C16CER vs. CER:LEF 1 H                        | >0.9999 | ns   |
| C16CER vs. ETOH:Lef 24 h                      | <0.0001 | **** |
| C16CER vs. CER:Lef 24 H                       | <0.0001 | **** |
| ETOH:Lef 1 h vs. CER:LEF 1 H                  | <0.0001 | **** |
| ETOH:Lef 1 h vs. ETOH:Lef 24 h                | 0.9734  | ns   |
| ETOH:Lef 1 h vs. CER:Lef 24 H                 | 0.9989  | ns   |
| CER:LEF 1 H vs. ETOH:Lef 24 h                 | <0.0001 | **** |
| CER:LEF 1 H vs. CER:Lef 24 H                  | <0.0001 | **** |
| ETOH:Lef 24 h vs. CER:Lef 24 H                | 0.4144  | ns   |
| Figure EV2G                                   |         |      |
| ETOH vs. C16CER                               | <0.0001 | **** |
| ETOH vs. ETOH:Lef 1 h                         | 0.7502  | ns   |
| ETOH vs. CER:LEF 1 H                          | <0.0001 | **** |
| ETOH vs. ETOH:Lef 24 h                        | 0.0063  | **   |
| ETOH vs. CER:Lef 24 H                         | 0.0562  | ns   |
| C16CER vs. ETOH:Lef 1 h                       | <0.0001 | **** |
| C16CER vs. CER:LEF 1 H                        | 0.9806  | ns   |
| C16CER vs. ETOH:Lef 24 h                      | <0.0001 | **** |
| C16CER vs. CER:Lef 24 H                       | <0.0001 | **** |
| ETOH:Lef 1 h vs. CER:LEF 1 H                  | <0.0001 | **** |
| ETOH:Lef 1 h vs. ETOH:Lef 24 h                | 0.2495  | ns   |
| ETOH:Lef 1 h vs. CER:Lef 24 H                 | 0.6842  | ns   |
| CER:LEF 1 H vs. ETOH:Lef 24 h                 | <0.0001 | **** |
| CER:LEF 1 H vs. CER:Lef 24 H                  | <0.0001 | **** |
| ETOH:Lef 24 h vs. CER:Lef 24 H                | 0.9801  | ns   |
| Figure EV2H                                   |         |      |
| ETOH vs. C16CER                               | <0.0001 | **** |
| ETOH vs. ETOH:Lef 1 h                         | >0.9999 | ns   |
| ETOH vs. CER:LEF 1 H                          | <0.0001 | **** |
| ETOH vs. ETOH:Lef 24 h                        | >0.9999 | ns   |
| ETOH vs. CER:Lef 24 H                         | 0.9398  | ns   |
| C16CER vs. ETOH:Lef 1 h                       | <0.0001 | **** |
| C16CER vs. CER:LEF 1 H                        | >0.9999 | ns   |
| C16CER vs. ETOH:Lef 24 h                      | <0.0001 | **** |
| C16CER vs. CER:Lef 24 H                       | <0.0001 | **** |
| ETOH:Lef 1 h vs. CER:LEF 1 H                  | <0.0001 | **** |
| ETOH:Lef 1 h vs. ETOH:Lef 24 h                | >0.9999 | ns   |
| ETOH:Lef 1 h vs. CER:Lef 24 H                 | 0.888   | ns   |
| CER:LEF 1 H vs. ETOH:Lef 24 h                 | <0.0001 | **** |
| CER:LEF 1 H vs. CER:Lef 24 H                  | <0.0001 | **** |
| ETOH:Lef 24 h vs. CER:Lef 24 H                | 0.8578  | ns   |
| Figure EV2J                                   |         |      |
| ETOH vs. C16-CER                              | <0.0001 | **** |
| ETOH vs. ETOH:P110 1 h at 10 uM               | 0.9974  | ns   |
| ETOH vs. CER:P110 10 UM 1 H                   | <0.0001 | **** |
| ETOH vs. ETOH:P110 12 h                       | 0.8708  | ns   |
| ETOH vs. CER:P110 12h                         | 0.0004  | ***  |
| C16-CER vs. ETOH:P110 1 h at 10 uM            | <0.0001 | **** |
| C16-CER vs. CER:P110 10 UM 1 H                | 0.2168  | ns   |
| C16-CER vs. ETOH:P110 12 h                    | <0.0001 | **** |
| C16-CER vs. CER:P110 12h                      | <0.0001 | **** |
| ETOH:P110 1 h at 10 uM vs. CER:P110 10 UM 1 H | <0.0001 | **** |
| ETOH:P110 1 h at 10 uM vs. ETOH:P110 12 h     | 0.9999  | ns   |
| ETOH:P110 1 h at 10 uM vs. CER:P110 12h       | 0.0001  | ***  |

|   |         |      |
|---|---------|------|
| CER:P110 10 UM 1 H vs. ETOH:P110 12 h         | <0.0001 | **** |
| CER:P110 10 UM 1 H vs. CER:P110 12h           | <0.0001 | **** |
| ETOH:P110 12 h vs. CER:P110 12h               | 0.0014  | **   |
| Figure EV2K                                   |         |      |
| ETOH vs. C16-CER                              | <0.0001 | **** |
| ETOH vs. ETOH:P110 1 h at 10 uM               | >0.9999 | ns   |
| ETOH vs. CER:P110 10 UM 1 H                   | <0.0001 | **** |
| ETOH vs. ETOH:P110 12 h                       | 0.8591  | ns   |
| ETOH vs. CER:P110 12h                         | >0.9999 | ns   |
| C16-CER vs. ETOH:P110 1 h at 10 uM            | <0.0001 | **** |
| C16-CER vs. CER:P110 10 UM 1 H                | 0.6603  | ns   |
| C16-CER vs. ETOH:P110 12 h                    | <0.0001 | **** |
| C16-CER vs. CER:P110 12h                      | <0.0001 | **** |
| ETOH:P110 1 h at 10 uM vs. CER:P110 10 UM 1 H | <0.0001 | **** |
| ETOH:P110 1 h at 10 uM vs. ETOH:P110 12 h     | 0.9729  | ns   |
| ETOH:P110 1 h at 10 uM vs. CER:P110 12h       | >0.9999 | ns   |
| CER:P110 10 UM 1 H vs. ETOH:P110 12 h         | <0.0001 | **** |
| CER:P110 10 UM 1 H vs. CER:P110 12h           | <0.0001 | **** |
| ETOH:P110 12 h vs. CER:P110 12h               | 0.8473  | ns   |
| Figure EV2L                                   |         |      |
| ETOH vs. C16-CER                              | <0.0001 | **** |
| ETOH vs. ETOH:P110 1 h at 10 uM               | 0.3298  | ns   |
| ETOH vs. CER:P110 10 UM 1 H                   | <0.0001 | **** |
| ETOH vs. ETOH:P110 12 h                       | 0.7725  | ns   |
| ETOH vs. CER:P110 12h                         | 0.5592  | ns   |
| C16-CER vs. ETOH:P110 1 h at 10 uM            | <0.0001 | **** |
| C16-CER vs. CER:P110 10 UM 1 H                | 0.0506  | ns   |
| C16-CER vs. ETOH:P110 12 h                    | <0.0001 | **** |
| C16-CER vs. CER:P110 12h                      | <0.0001 | **** |
| ETOH:P110 1 h at 10 uM vs. CER:P110 10 UM 1 H | <0.0001 | **** |
| ETOH:P110 1 h at 10 uM vs. ETOH:P110 12 h     | 0.9812  | ns   |
| ETOH:P110 1 h at 10 uM vs. CER:P110 12h       | 0.9991  | ns   |
| CER:P110 10 UM 1 H vs. ETOH:P110 12 h         | <0.0001 | **** |
| CER:P110 10 UM 1 H vs. CER:P110 12h           | <0.0001 | **** |
| ETOH:P110 12 h vs. CER:P110 12h               | 0.9994  | ns   |
| Figure EV2N                                   |         |      |
| BSA vs. PAL                                   | <0.0001 | **** |
| BSA vs. BSA:WFA                               | >0.9999 | ns   |
| BSA vs. PAL:WFA                               | <0.0001 | **** |
| BSA vs. BSA:CEL                               | <0.0001 | **** |
| BSA vs. PAL:CEL                               | <0.0001 | **** |
| PAL vs. BSA:WFA                               | <0.0001 | **** |
| PAL vs. PAL:WFA                               | 0.9963  | ns   |
| PAL vs. BSA:CEL                               | 0.9178  | ns   |
| PAL vs. PAL:CEL                               | 0.0651  | ns   |
| BSA:WFA vs. PAL:WFA                           | <0.0001 | **** |
| BSA:WFA vs. BSA:CEL                           | <0.0001 | **** |
| BSA:WFA vs. PAL:CEL                           | <0.0001 | **** |
| PAL:WFA vs. BSA:CEL                           | >0.9999 | ns   |
| PAL:WFA vs. PAL:CEL                           | 0.4601  | ns   |
| BSA:CEL vs. PAL:CEL                           | 0.9545  | ns   |
| Figure EV2O                                   |         |      |
| BSA vs. PAL                                   | <0.0001 | **** |
| BSA vs. BSA:WFA                               | 0.8747  | ns   |
| BSA vs. PAL:WFA                               | <0.0001 | **** |
| BSA vs. BSA:CEL                               | <0.0001 | **** |
| BSA vs. PAL:CEL                               | <0.0001 | **** |
| PAL vs. BSA:WFA                               | <0.0001 | **** |
| PAL vs. PAL:WFA                               | <0.0001 | **** |
| PAL vs. BSA:CEL                               | 0.0634  | ns   |
| PAL vs. PAL:CEL                               | 0.014   | *    |
| BSA:WFA vs. PAL:WFA                           | <0.0001 | **** |
| BSA:WFA vs. BSA:CEL                           | <0.0001 | **** |
| BSA:WFA vs. PAL:CEL                           | <0.0001 | **** |

|                                 |         |      |
|---------------------------------|---------|------|
| PAL:WFA vs. BSA:CEL             | 0.3491  | ns   |
| PAL:WFA vs. PAL:CEL             | 0.4251  | ns   |
| BSA:CEL vs. PAL:CEL             | >0.9999 | ns   |
| Figure EV2P                     |         |      |
| BSA vs. PAL                     | <0.0001 | **** |
| BSA vs. BSA:WFA                 | 0.0335  | *    |
| BSA vs. PAL:WFA                 | <0.0001 | **** |
| BSA vs. BSA:CEL                 | <0.0001 | **** |
| BSA vs. PAL:CEL                 | <0.0001 | **** |
| PAL vs. BSA:WFA                 | <0.0001 | **** |
| PAL vs. PAL:WFA                 | 0.1968  | ns   |
| PAL vs. BSA:CEL                 | 0.3089  | ns   |
| PAL vs. PAL:CEL                 | 0.0201  | *    |
| BSA:WFA vs. PAL:WFA             | <0.0001 | **** |
| BSA:WFA vs. BSA:CEL             | <0.0001 | **** |
| BSA:WFA vs. PAL:CEL             | <0.0001 | **** |
| PAL:WFA vs. BSA:CEL             | 0.9999  | ns   |
| PAL:WFA vs. PAL:CEL             | 0.9503  | ns   |
| BSA:CEL vs. PAL:CEL             | 0.8724  | ns   |
| Figure EV2R                     |         |      |
| DMSO vs. FCCP                   | <0.0001 | **** |
| DMSO vs. DMSO:893               | 0.408   | ns   |
| DMSO vs. FCCP:893               | <0.0001 | **** |
| FCCP vs. DMSO:893               | <0.0001 | **** |
| FCCP vs. FCCP:893               | 0.2613  | ns   |
| DMSO:893 vs. FCCP:893           | <0.0001 | **** |
| Figure EV2S                     |         |      |
| DMSO vs. FCCP                   | <0.0001 | **** |
| DMSO vs. DMSO:893               | 0.9997  | ns   |
| DMSO vs. FCCP:893               | <0.0001 | **** |
| FCCP vs. DMSO:893               | <0.0001 | **** |
| FCCP vs. FCCP:893               | 0.3234  | ns   |
| DMSO:893 vs. FCCP:893           | <0.0001 | **** |
| Figure EV2T                     |         |      |
| DMSO vs. FCCP                   | <0.0001 | **** |
| DMSO vs. DMSO:893               | 0.4076  | ns   |
| DMSO vs. FCCP:893               | <0.0001 | **** |
| FCCP vs. DMSO:893               | <0.0001 | **** |
| FCCP vs. FCCP:893               | 0.9125  | ns   |
| DMSO:893 vs. FCCP:893           | <0.0001 | **** |
| Figure EV4A                     |         |      |
| 1                               | 0.1513  | ns   |
| 2                               | 0.9172  | ns   |
| 3                               | 0.2733  | ns   |
| 4                               | 0.5713  | ns   |
| Figure EV4B                     |         |      |
| 1                               | 0.1411  | ns   |
| 2                               | 0.6381  | ns   |
| 3                               | 0.0013  | **   |
| 4                               | 0.8549  | ns   |
| Figure EV4E                     |         |      |
|                                 | 0.8596  | ns   |
| Figure EV4F                     |         |      |
| SD vs. HFD:VEH                  | 0.225   | ns   |
| SD vs. HFD:893                  | <0.0001 | **** |
| SD vs. HFD:VEH:WHEEL            | 0.0286  | *    |
| SD vs. HFD:893:WHEEL            | <0.0001 | **** |
| HFD:VEH vs. HFD:893             | <0.0001 | **** |
| HFD:VEH vs. HFD:VEH:WHEEL       | <0.0001 | **** |
| HFD:VEH vs. HFD:893:WHEEL       | <0.0001 | **** |
| HFD:893 vs. HFD:VEH:WHEEL       | 0.1764  | ns   |
| HFD:893 vs. HFD:893:WHEEL       | 0.0176  | *    |
| HFD:VEH:WHEEL vs. HFD:893:WHEEL | <0.0001 | **** |



|   |         |      |
|---|---------|------|
| Figure EV4G   |         |      |
| Standard Diet vs. HFD + Vehicle                     | <0.0001 | **** |
| Standard Diet vs. HFD + 120 mpk 893                 | 0.9516  | ns   |
| Standard Diet vs. HFD + Vehicle + Wheel             | 0.2118  | ns   |
| Standard Diet vs. HFD + 120 mpk 893 + Wheel         | 0.8166  | ns   |
| HFD + Vehicle vs. HFD + 120 mpk 893                 | <0.0001 | **** |
| HFD + Vehicle vs. HFD + Vehicle + Wheel             | 0.0027  | **   |
| HFD + Vehicle vs. HFD + 120 mpk 893 + Wheel         | <0.0001 | **** |
| HFD + 120 mpk 893 vs. HFD + Vehicle + Wheel         | 0.5707  | ns   |
| HFD + 120 mpk 893 vs. HFD + 120 mpk 893 + Wheel     | 0.4469  | ns   |
| HFD + Vehicle + Wheel vs. HFD + 120 mpk 893 + Wheel | 0.0415  | *    |
| Figure EV4H   |         |      |
| SD vs. HFD:VEH                                      | 0.8945  | ns   |
| SD vs. HFD:893                                      | <0.0001 | **** |
| SD vs. HFD:VEH:WHEEL                                | 0.0097  | **   |
| SD vs. HFD:893:WHEEL                                | <0.0001 | **** |
| HFD:VEH vs. HFD:893                                 | 0.001   | ***  |
| HFD:VEH vs. HFD:VEH:WHEEL                           | 0.08    | ns   |
| HFD:VEH vs. HFD:893:WHEEL                           | <0.0001 | **** |
| HFD:893 vs. HFD:VEH:WHEEL                           | 0.6315  | ns   |
| HFD:893 vs. HFD:893:WHEEL                           | 0.3563  | ns   |
| HFD:VEH:WHEEL vs. HFD:893:WHEEL                     | 0.0351  | *    |
| Figure EV4I   |         |      |
| SD vs. HFD:VEH                                      | 0.6908  | ns   |
| SD vs. HFD:893                                      | 0.8936  | ns   |
| SD vs. HFD:VEH:WHEEL                                | 0.9952  | ns   |
| SD vs. HFD:893:WHEEL                                | 0.9258  | ns   |
| HFD:VEH vs. HFD:893                                 | 0.1984  | ns   |
| HFD:VEH vs. HFD:VEH:WHEEL                           | 0.9149  | ns   |
| HFD:VEH vs. HFD:893:WHEEL                           | 0.3144  | ns   |
| HFD:893 vs. HFD:VEH:WHEEL                           | 0.7303  | ns   |
| HFD:893 vs. HFD:893:WHEEL                           | >0.9999 | ns   |
| HFD:VEH:WHEEL vs. HFD:893:WHEEL                     | 0.7989  | ns   |
| Figure EV5A   |         |      |
| d17:1/22:0  |         |      |
| sd vs. hfd  | 0.9991  | ns   |
| sd vs. hfd 893                                      | 0.3733  | ns   |
| hfd vs. hfd 893                                     | 0.3921  | ns   |
| d18:1/16:0  |         |      |
| sd vs. hfd  | 0.5856  | ns   |
| sd vs. hfd 893                                      | 0.1777  | ns   |
| hfd vs. hfd 893                                     | 0.6277  | ns   |
| d18:1/18:0  |         |      |
| sd vs. hfd  | 0.4583  | ns   |
| sd vs. hfd 893                                      | 0.8782  | ns   |
| hfd vs. hfd 893                                     | 0.4694  | ns   |
| d18:1/20:0  |         |      |
| sd vs. hfd  | 0.9985  | ns   |
| sd vs. hfd 893                                      | 0.3002  | ns   |
| hfd vs. hfd 893                                     | 0.3212  | ns   |
| d18:1/22:0  |         |      |
| sd vs. hfd  | 0.9945  | ns   |
| sd vs. hfd 893                                      | 0.3381  | ns   |
| hfd vs. hfd 893                                     | 0.3835  | ns   |
| d18:1/22:1  |         |      |
| sd vs. hfd  | 0.9479  | ns   |
| sd vs. hfd 893                                      | 0.3291  | ns   |
| hfd vs. hfd 893                                     | 0.4808  | ns   |
| d18:1/23:0  |         |      |
| sd vs. hfd  | 0.9665  | ns   |
| sd vs. hfd 893                                      | 0.1742  | ns   |
| hfd vs. hfd 893                                     | 0.2483  | ns   |
| d18:1/24:0  |         |      |
| sd vs. hfd  | 0.9907  | ns   |

|                 |        |    |
|-----------------|--------|----|
| sd vs. hfd 893  | 0.2412 | ns |
| hfd vs. hfd 893 | 0.2881 | ns |
| d18:1/24:1      |        |    |
| sd vs. hfd      | 0.9854 | ns |
| sd vs. hfd 893  | 0.2049 | ns |
| hfd vs. hfd 893 | 0.2577 | ns |
| d18:2/18:0      |        |    |
| sd vs. hfd      | 0.3536 | ns |
| sd vs. hfd 893  | 0.7674 | ns |
| hfd vs. hfd 893 | 0.1317 | ns |
| d18:2/22:0      |        |    |
| sd vs. hfd      | 0.8879 | ns |
| sd vs. hfd 893  | 0.3194 | ns |
| hfd vs. hfd 893 | 0.5542 | ns |
| d18:2/24:1      |        |    |
| sd vs. hfd      | 0.795  | ns |
| sd vs. hfd 893  | 0.2207 | ns |
| hfd vs. hfd 893 | 0.5062 | ns |