

## Supplemental Information

### Chemical Hybridization of Glucagon and Thyroid Hormone Optimizes Therapeutic Impact for Metabolic Disease

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**Table S1. Blood Parameters After 3 weeks of Treatment in CD-HFD Mice**

|                                   | Vehicle                                   | Glucagon/T <sub>3</sub>                     |
|-----------------------------------|---|---|
| Hematocrite (%)                   | 44.92 ± 0.59                              | 46.08 ± 0.59                                |
| Hemoglobin (g dl <sup>-1</sup> )  | 14.09 ± 0.27                              | 13.85 ± 0.16                                |
| Erythrocyte (# μl <sup>-1</sup> ) | 9.8x10 <sup>7</sup> ± 0.3x10 <sup>7</sup> | 9.5x10 <sup>7</sup> ± 0.1x10 <sup>7</sup>   |
| MCH (pg)                          | 16.92 ± 0.34                              | 16.62 ± 0.30                                |
| MCV (fl)                          | 53.67 ± 0.83                              | 56.59 ± 0.34*                               |
| Leukocyte (# μl <sup>-1</sup> )   | 9.0x10 <sup>4</sup> ± 1.3x10 <sup>4</sup> | 8.0x10 <sup>4</sup> ± 0.8x10 <sup>4</sup>   |
| Thrombocyte (# μl <sup>-1</sup> ) | 2.3x10 <sup>7</sup> ± 0.9x10 <sup>7</sup> | 1.8x10 <sup>7</sup> ± 0.1x10 <sup>7</sup> * |
| Neutrophil (# μl <sup>-1</sup> )  | 9.5x10 <sup>3</sup> ± 2.1x10 <sup>3</sup> | 8.5x10 <sup>3</sup> ± 1.1x10 <sup>3</sup>   |
| Eosinophil (# μl <sup>-1</sup> )  | 1400 ± 319.5                              | 670.8 ± 120.3                               |
| Basophil (# μl <sup>-1</sup> )    | 262.5 ± 87.5                              | 320.8 ± 55.9                                |
| Monocyte (# μl <sup>-1</sup> )    | 4.9x10 <sup>3</sup> ± 0.9x10 <sup>3</sup> | 5.8x10 <sup>3</sup> ± 1.4x10 <sup>3</sup>   |
| Lymphocyte (# μl <sup>-1</sup> )  | 7.4x10 <sup>4</sup> ± 1.1x10 <sup>4</sup> | 6.4x10 <sup>4</sup> ± 0.7x10 <sup>4</sup>   |

**Table S2. Cardiac Parameters After 4 weeks of Treatment**

|                              | Vehicle         | Glucagon       | T <sub>3</sub>    | Glucagon/T <sub>3</sub> |
|------------------------------|-----------------|----------------|-------------------|-------------------------|
| BW (g)                       | 42.24 ± 5.95    | 39.13 ± 4.07   | 34.93 ± 2.54      | 39.95 ± 3.99            |
| HW (mg)                      | 200.80 ± 23.78  | 193.40 ± 32.21 | 289.00 ± 18.62*** | 226.50 ± 28.97          |
| BW/HW (mg g <sup>-1</sup> )  | 4.84 ± 0.85     | 5.01 ± 1.07    | 8.29 ± 0.47***    | 5.68 ± 0.62             |
| TL (mm)                      | 19.47 ± 0.35    | 19.27 ± 0.37   | 19.36 ± 0.24      | 19.29 ± 0.24            |
| HW/TL (mg mm <sup>-1</sup> ) | 10.31 ± 1.17    | 10.03 ± 1.60   | 14.93 ± 1.03***   | 11.73 ± 1.39            |
| LVIDd (mm)                   | 2.92 ± 0.32     | 2.80 ± 0.34    | 3.56 ± 0.67*      | 3.10 ± 0.37             |
| LVIDs (mm)                   | 1.60 ± 0.32     | 1.46 ± 0.31    | 2.23 ± 0.80*      | 1.59 ± 0.33             |
| IVSd (mm)                    | 0.56 ± 0.02     | 0.56 ± 0.02    | 0.54 ± 0.03       | 0.55 ± 0.03             |
| IVSs (mm)                    | 0.57 ± 0.03     | 0.55 ± 0.02    | 0.55 ± 0.02       | 0.54 ± 0.02             |
| PWTd (mm)                    | 0.53 ± 0.02     | 0.52 ± 0.02    | 0.54 ± 0.03       | 0.53 ± 0.02             |
| PWTs (mm)                    | 0.54 ± 0.02     | 0.52 ± 0.03    | 0.54 ± 0.02       | 0.51 ± 0.02             |
| LVM (mg)                     | 36.66 ± 6.33    | 34.23 ± 6.85   | 51.49 ± 14.50***  | 39.92 ± 9.54            |
| HR (bpm)                     | 658.60 ± 102.04 | 614.83 ± 75.32 | 532.46 ± 108.32*  | 636.89 ± 94.42          |
| RR (1/min)                   | 243.32 ± 31.70  | 223.59 ± 28.31 | 318.34 ± 42.28**  | 243.99 ± 62.88          |
| EF (%)                       | 78.77 ± 9.44    | 81.90 ± 5.60   | 69.76 ± 14.37     | 81.71 ± 6.42            |
| FS (%)                       | 47.23 ± 9.45    | 49.51 ± 6.11   | 39.77 ± 11.42     | 49.79 ± 6.95            |
| SV (μl)                      | 25.99 ± 5.17    | 25.06 ± 5.96   | 35.25 ± 8.19*     | 31.07 ± 8.29            |
| CO (ml/min)                  | 17.06 ± 4.24    | 15.30 ± 3.70   | 18.22 ± 2.67      | 19.26 ± 3.37            |

**Table S3. Taqman Primers Used for qPCR**

| Target        | ID            | Target        | ID            | Target       | ID            |
|---------------|---------------|---------------|---------------|--------------|---------------|
| <i>Pck1</i>   | Mm01247058_m1 | <i>ApoE</i>   | Mm00437573_m1 | <i>Pgc1a</i> | Mm01208835_m1 |
| <i>G6pc</i>   | Mm00839363_m1 | <i>Ldlr</i>   | Mm00440169_m1 | <i>Dio2</i>  | Mm00515664_m1 |
| <i>Nr3c1</i>  | Mm00433832_m1 | <i>Scarb1</i> | Mm00450236_m1 | <i>Hprt</i>  | Mm01545399_m1 |
| <i>Pklr</i>   | Mm00443090_m1 | <i>Pgc1b</i>  | Mm00504720_m1 | <i>Thrb</i>  | Mm00437044_m1 |
| <i>Hnf4a</i>  | Mm01247712_m1 | <i>Gck</i>    | Mm00439129_m1 | <i>Ucp1</i>  | Mm01244861_m1 |
| <i>Pdk4</i>   | Mm00443325_m1 | <i>Pklr</i>   | Mm00443090_m1 | <i>Fgf21</i> | Mm00840165_g1 |
| <i>Fasn</i>   | Mm00662322_g1 | <i>Ppara</i>  | Mm00440939_m1 | <i>Thra</i>  | Mm00579691_m1 |
| <i>Hsl</i>    | Mm00495359_m1 | <i>Me</i>     | Mm00782380_s1 | <i>Dio1</i>  | Mm00839358_m1 |
| <i>Srebp2</i> | Mm01306292_m1 | <i>Cyp7a1</i> | Mm00484150_m1 | <i>Dgat</i>  | Mm00515643_m1 |
| <i>Cpt1a</i>  | Mm01231183_m1 | <i>Apoa1</i>  | Mm00437569_m1 | <i>Gcgr</i>  | Mm00433546_m1 |
| <i>Glut2</i>  | Mm00446229_m1 | <i>Hmgcr</i>  | Mm01282499_m1 | <i>Lipc</i>  | Mm01171487_m1 |
| <i>Lcat</i>   | Mm01247340_m1 | <i>Pcsk9</i>  | Mm01263610_m1 | <i>Nppa</i>  | Mm01255747_g1 |
| <i>Nppb</i>   | Mm01255770_g1 | <i>Ucp2</i>   | Mm00627599_m1 |              |               |