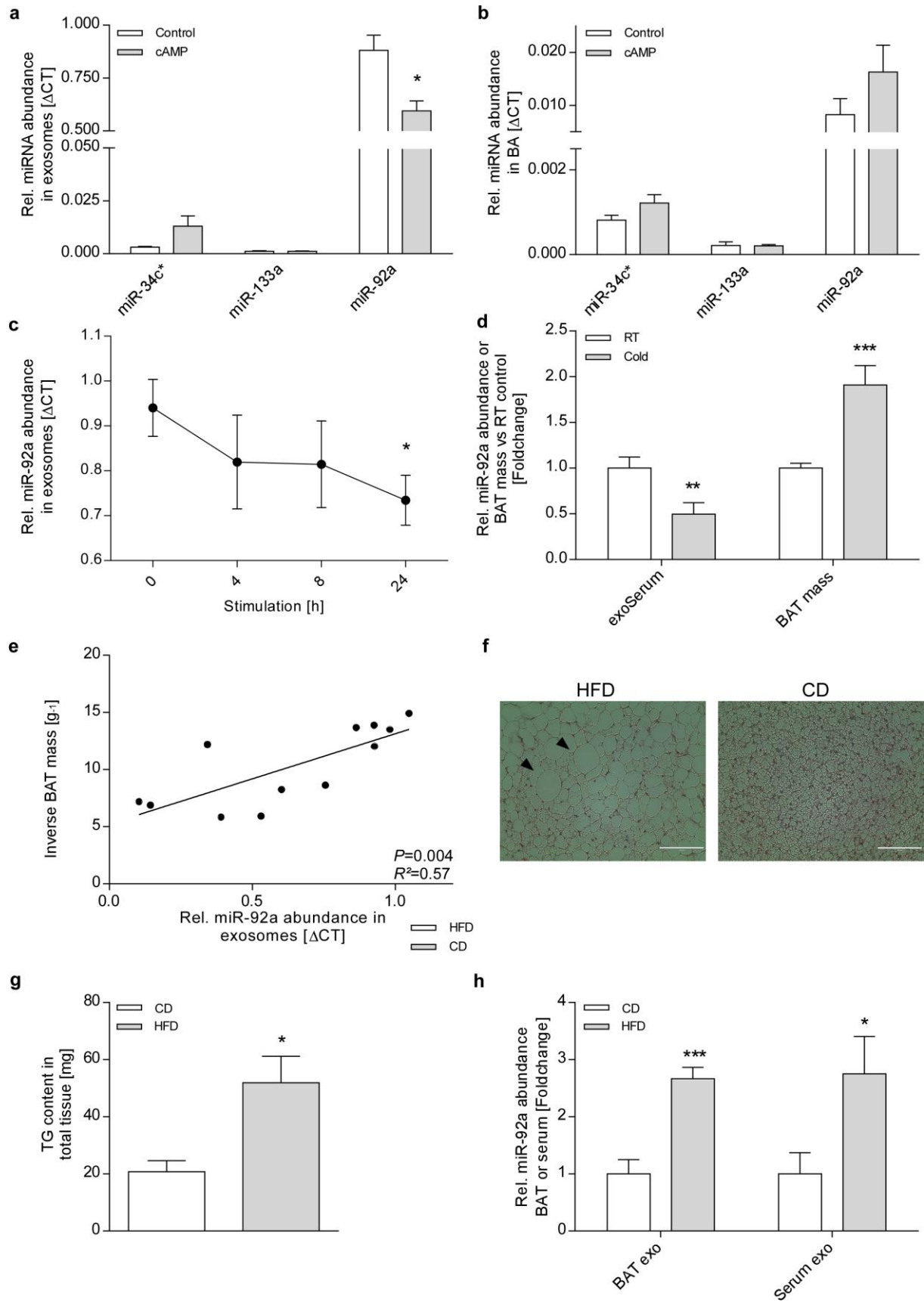


**Supplementary Figure 1 Analysis of beige fat and cells and characteristics of exosome release, related to Figure 1**

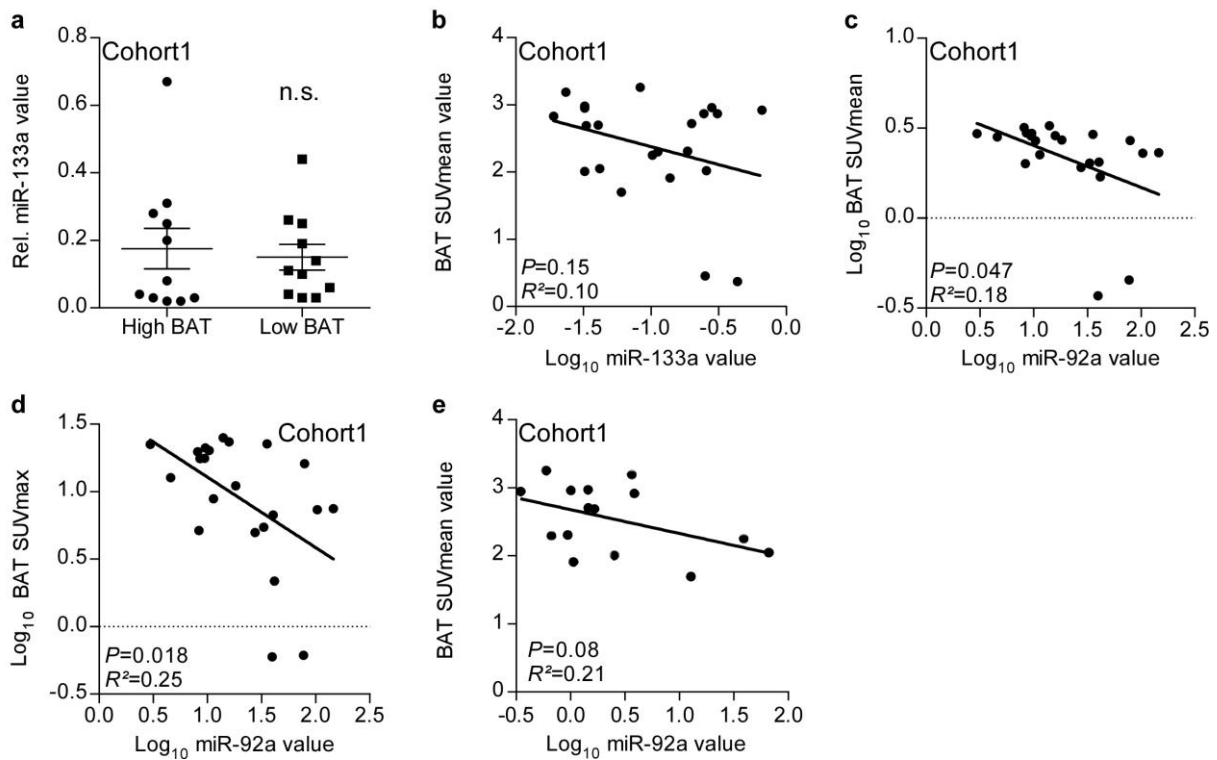
(a) Fold-change in UCP-1 mRNA abundance in white adipocytes upon  $\beta$ -adrenergic stimulation (NE) or WAT depots after cold exposure in mice compared to untreated cells or control tissue from mice at room temperature (RT). (b) Qualitative Western blot analysis of CD63, Hsp70 and Tubulin positive particles released from tissues and Cyt-c as cellular negative control ( $n=1$ ). The exosomes were released from mice tissues exposed to cold (4°C) compared to RT controls. (c) Tissue weights of cold exposed mice and controls (RT). (d) Absolute exosome numbers released from fat tissues of cold exposed mice and RT controls (RT). (e) Clustering of exosomal miRNAs. Hierarchical clustering of miRNAs in exosomes isolated from serum of mice either exposed to cold (cold) or treated with the  $\beta_3$  receptor agonist CL-316,243 (CL) compared to vehicle injected control mice (wt), as well as of miRNAs in exosomes released from brown adipocytes (BA) treated with cAMP (cAMP) or untreated

control cells (wt). Values are expressed as mean  $\pm$  s.e.m. (unpaired, two-tailed *t*-test,  $P^*\leq 0.05$ ,  $**P\leq 0.01$ ,  $***P\leq 0.001$ ,  $n=6$  mice per group or  $n=3$  for cells).



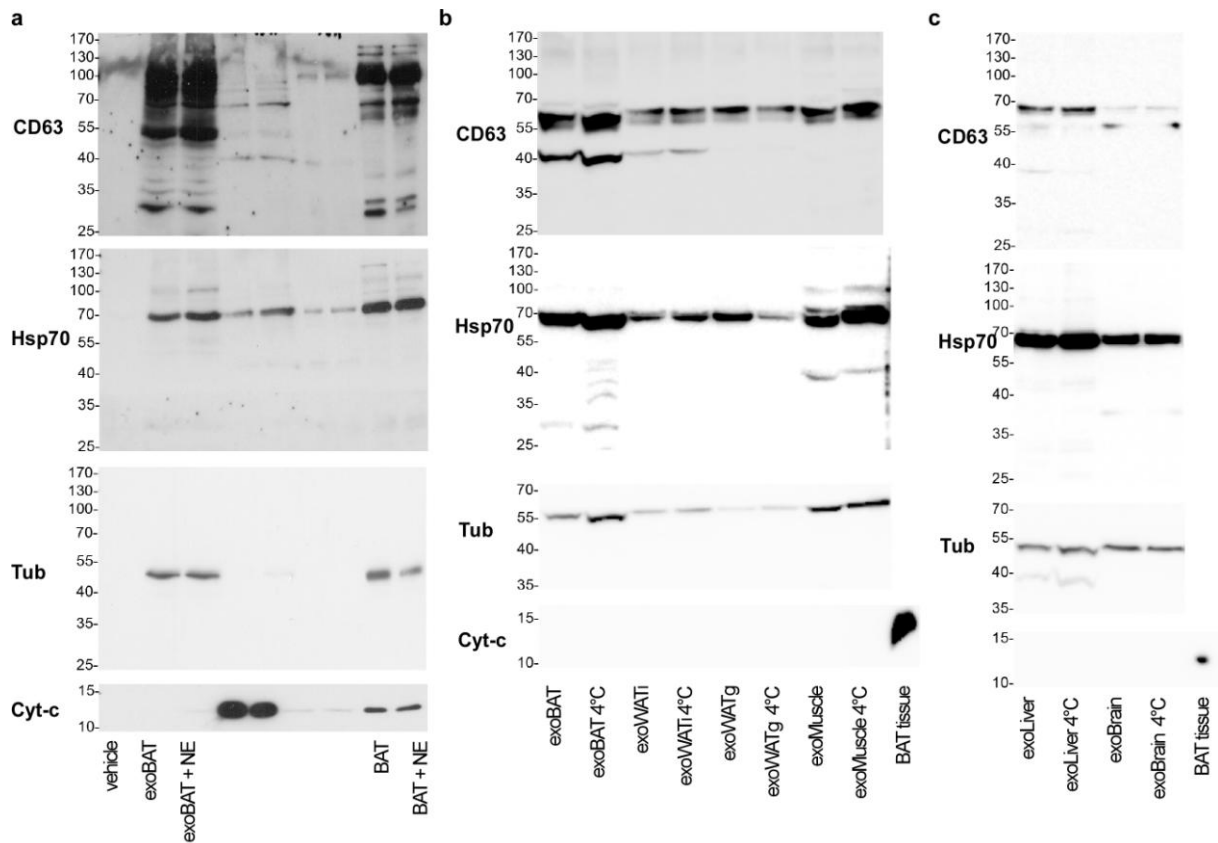
Supplementary Figure 2 Validation of miRNA candidates and HFD study, related to Figure 2

(**a** and **b**) qPCR analysis of the miRNA candidates present in exosomes(**a**) released from untreated (wild type) and cAMP-treated (200  $\mu$ M) cells, as compared to the cellular miRNA expression (**b**) without and with cAMP treatment (200  $\mu$ M). (**c**) Time-course of exosomal miR-92a release from brown adipocytes after cAMP stimulation. (**d**) Relative miR-92a abundance in mouse serum and BAT mass compared to cold exposure. (**e**) Inverse correlation of BAT mass with exosomal miR-92a abundance in mice, (Pearson's correlation,  $R^2=0.57$ ,  $P=0.004$ ,  $n=12$ ). (**f**) H&E Staining of paraffin-sections of 16 week HFD and CD mice, large lipid droplets are indicated by black arrows (Scale bar: 100  $\mu$ m). (**g**) BAT triglyceride content after 16 week HFD and CD mice (**h**) Total release of exosomal miR-92a from BAT tissues or serum of 16 week HFD mice versus CD mice. Values present mean  $\pm$  s.e.m. (unpaired, two-tailed  $t$ -test,  $*P\leq 0.05$ ,  $**P\leq 0.01$ ,  $***P\leq 0.001$ ,  $n=5-6$  mice per group or  $n=3$  for cells).



**Supplementary Figure 3 Detailed analysis of miR-133a and miR-92a in exosomes from human serum, related to Figure 3**

(a) miR-133a expression in human serum quantified by qPCR. Data was normalized to U6, and is presented as mean  $\pm$  s.e.m. (unpaired, two-tailed *t*-test, n.s., not significant,  $n=11$  per group). (b)  $\text{Log}_{10}$  miR-133a value is not related to BAT SUVmean value (Pearson's correlation,  $R^2=0.10$ ,  $P=0.15$ ,  $n=22$ ). (c) Correlation of  $\text{Log}_{10}$  transformed BAT SUVmean and  $\text{Log}_{10}$  miR-92a (Pearson's correlation,  $R^2=0.18$ ,  $P=0.047$ ,  $n=22$ ); related to Fig. 3c. (d)  $\text{Log}_{10}$  BAT SUVmax and  $\text{Log}_{10}$  miR-92a correlation (Pearson's correlation,  $R^2=0.25$ ,  $P=0.018$ ,  $n=22$ ); related to Fig. 3d. (e) Correlation of BAT SUVmean and  $\text{Log}_{10}$  miR-92a of acutely cold exposed subjects (Pearson's correlation,  $R^2=0.21$ ,  $P=0.08$ ,  $n=15$ )



**Supplementary Figure 4 Full display of Western blots, related to Figure 1 and Supplementary Figure 1**

(a) Complete immunoblots of CD63, Hsp70, Tubulin (Tub) and Cytochrome-C (Cyt-c) utilized in Fig. 1b. Complete immunoblots of CD63, Hsp70, Tubulin (Tub) and Cytochrome-C (Cyt-c) utilized in Supplementary Fig. 1b (b) and (c).

| miRNA candidates        | cold  | CL    | cAMP |
|-------------------------|-------|-------|------|
| mmu-miR-27a-000408      | 65.93 | 1.00  |      |
| hsa-miR-149-002255      | 35.87 | 1.00  | 4.97 |
| hsa-miR-93#-002139      | 31.30 | 0.67  | 3.94 |
| mmu-miR-494-002365      | 20.20 | 1.00  | 1.75 |
| mmu-miR-881-002609      | 19.25 | 11.18 | 0.11 |
| rno-miR-146B-002755     | 16.93 | 1.56  |      |
| mmu-miR-31-000185       | 16.63 | 1.00  |      |
| mmu-miR-142-3p-000464   | 15.19 | 46.02 |      |
| mmu-miR-876-3p-002464   | 14.32 | 1.00  |      |
| mmu-miR-199a-3p-002304  | 12.98 | 0.25  |      |
| rno-miR-450a-001345     | 11.95 | 1.00  |      |
| mmu-miR-204-000508      | 11.64 | 1.00  |      |
| mmu-miR-203-000507      | 10.44 | 0.89  | 0.05 |
| mmu-miR-200b-002251     | 10.17 | 1.00  |      |
| mmu-let-7e-002406       | 9.44  | 35.19 |      |
| mmu-miR-670-002020      | 8.89  | 3.04  | 4.96 |
| mmu-miR-21-000397       | 6.32  | 1.00  |      |
| mmu-miR-200c-002300     | 6.05  | 1.00  | 0.55 |
| mmu-miR-20a-000580      | 5.08  | 3.09  |      |
| mmu-let-7g-002282       | 4.92  | 1.38  |      |
| mmu-miR-34c#-002584     | 4.42  | 40.10 | 8.72 |
| mmu-miR-145-002278      | 4.28  | 1.91  |      |
| mmu-miR-30d-000420      | 4.18  | 1.44  |      |
| mmu-miR-296-5p-000527   | 4.12  | 1.00  |      |
| rno-miR-743b-002068     | 3.98  | 6.14  | 1.45 |
| mmu-miR-2146-241082_mat | 3.72  | 2.64  |      |
| hsa-miR-493-3p-001282   | 3.18  | 2.38  |      |
| rno-miR-347-001334      | 3.12  | 0.38  |      |
| mmu-miR-26a-000405      | 3.09  | 1.68  |      |
| mmu-miR-125b-3p-002378  | 3.08  | 1.42  |      |
| mmu-miR-30a-000417      | 2.87  | 9.35  |      |
| mmu-miR-210-000512      | 2.75  | 1.65  | 0.13 |
| mmu-miR-193b-002467     | 2.60  | 0.37  | 1.91 |
| mmu-miR-195-000494      | 2.55  | 9.64  | 1.98 |
| mmu-miR-432-241135_mat  | 2.40  | 1.16  |      |
| mmu-miR-106b-000442     | 2.37  | 2.59  |      |
| mmu-miR-26b-000407      | 2.36  | 2.02  |      |
| mmu-miR-186-002285      | 2.34  | 0.40  |      |
| hsa-miR-340-000550      | 2.18  | 1.00  |      |
| mmu-miR-1896-121128_mat | 2.10  | 1.67  |      |
| mmu-miR-425-001516      | 2.05  | 11.13 |      |
| hsa-miR-421-002700      | 1.86  | 1.59  |      |
| mmu-miR-720-001629      | 1.80  | 1.37  |      |

|                            |      |       |       |
|----------------------------|------|-------|-------|
| mmu-miR-19b-000396         | 1.78 | 1.21  |       |
| mmu-miR-687-001674         | 1.75 | 1.00  |       |
| mmu-miR-30e-002223         | 1.70 | 1.34  | 80.42 |
| mmu-miR-741-002457         | 1.67 | 1.00  |       |
| mmu-miR-125a-5p-002198     | 1.61 | 1.40  |       |
| mmu-miR-652-002352         | 1.49 | 1.00  |       |
| mmu-miR-1937c-241011_mat   | 1.46 | 1.15  |       |
| mmu-miR-30b-000602         | 1.44 | 0.83  |       |
| mmu-miR-685-001670         | 1.42 | 1.05  | 2.09  |
| mmu-miR-1942-121136_mat    | 1.37 | 1.14  |       |
| mmu-miR-1188-002866        | 1.36 | 1.76  |       |
| mmu-miR-871-002354         | 1.35 | 1.00  |       |
| mmu-miR-484-001821         | 1.35 | 1.17  | 1.03  |
| mmu-miR-1894-3p-241002_mat | 1.34 | 1.38  |       |
| mmu-miR-1937b-241023_mat   | 1.34 | 1.08  |       |
| rno-miR-7#-001338          | 1.32 | 1.00  |       |
| mmu-miR-1897-5p-121199_mat | 1.30 | 0.61  |       |
| mmu-miR-673-001954         | 1.28 | 1.42  |       |
| mmu-miR-222-002276         | 1.24 | 0.77  | 27.87 |
| rno-miR-25#-002080         | 1.23 | 1.00  |       |
| mmu-miR-532-5p-001518      | 1.19 | 1.00  |       |
| mmu-miR-615-5p-002353      | 1.18 | 1.00  |       |
| mmu-miR-501-001356         | 1.18 | 1.00  |       |
| hsa-miR-423-3P-002626      | 1.14 | 1.94  |       |
| mmu-miR-463-002662         | 1.10 | 1.38  |       |
| mmu-miR-1191-002892        | 1.08 | 2.66  |       |
| mmu-miR-486-001278         | 1.06 | 0.70  |       |
| mmu-miR-1904-121162_mat    | 1.03 | 1.69  |       |
| mmu-miR-191-002299         | 1.03 | 0.88  | 3.10  |
| mmu-miR-30c-000419         | 1.02 | 0.14  |       |
| mmu-miR-151-3p-001190      | 1.00 | 10.71 |       |
| mmu-miR-339-3p-002533      | 1.00 | 10.42 | 27.63 |
| mmu-miR-669m-121190_mat    | 1.00 | 9.07  |       |
| mmu-miR-101b-002531        | 1.00 | 5.32  | 1.82  |
| mmu-miR-302a-000529        | 1.00 | 5.28  |       |
| mmu-miR-532-3p-002355      | 1.00 | 4.71  |       |
| mmu-miR-1971-121161_mat    | 1.00 | 4.22  |       |
| mmu-miR-297a#-002454       | 1.00 | 2.79  | 0.28  |
| mmu-miR-322-001059         | 1.00 | 2.13  |       |
| mmu-miR-883b-3p-002565     | 1.00 | 2.02  |       |
| mmu-miR-376c-002450        | 1.00 | 1.85  |       |
| mmu-miR-466k-240990_mat    | 1.00 | 1.56  |       |
| rno-miR-742-002055         | 1.00 | 1.22  |       |
| mmu-miR-331-5p-002233      | 1.00 | 1.15  |       |
| mmu-miR-697-001631         | 1.00 | 1.14  | 2.89  |
| hsa-miR-144-002676         | 1.00 | 1.04  |       |



|                           |      |       |       |
|---------------------------|------|-------|-------|
| U6 snRNA-001973           | 0.99 | 1.09  | 0.99  |
| mmu-miR-140-001187        | 0.98 | 0.98  |       |
| rno-miR-196c-002049       | 0.97 | 0.97  |       |
| hsa-miR-223-000526        | 0.96 | 0.92  |       |
| rno-miR-632-241110_mat    | 0.95 | 0.98  |       |
| mmu-miR-16-000391         | 0.93 | 0.76  | 1.42  |
| rno-miR-489-001353        | 0.92 | 1.22  | 0.74  |
| mmu-miR-2134-241120_mat   | 0.92 | 0.65  |       |
| mmu-miR-667-001949        | 0.91 | 1.92  | 0.29  |
| Mamm U6-001973            | 0.90 | 1.09  |       |
| mmu-miR-342-3p-002260     | 0.88 | 1.96  | 2.93  |
| hsa-miR-412-001023        | 0.87 | 2.63  |       |
| mmu-miR-374-5p-001319     | 0.87 | 2.43  |       |
| mmu-miR-409-3p-002332     | 0.84 | 0.40  | 0.33  |
| rno-miR-327-001328        | 0.84 | 1.30  |       |
| mmu-miR-1951-121165_mat   | 0.83 | 1.41  |       |
| mmu-miR-96-000186         | 0.82 | 0.82  |       |
| mmu-miR-139-5p-002289     | 0.82 | 0.39  |       |
| mmu-miR-543-001298        | 0.81 | 0.81  |       |
| mmu-miR-17-002308         | 0.81 | 0.47  |       |
| mmu-miR-467b-001671       | 0.81 | 0.81  |       |
| mmu-miR-146a-000468       | 0.81 | 0.81  | 3.85  |
| mmu-miR-488-001659        | 0.81 | 0.66  |       |
| mmu-miR-1905-121196_mat   | 0.80 | 0.83  |       |
| mmu-miR-196a#-002477      | 0.80 | 1.09  | 0.50  |
| mmu-miR-141#-002513       | 0.79 | 0.79  | 0.75  |
| mmu-miR-1982.1-121157_mat | 0.78 | 0.78  |       |
| mmu-miR-1956-121129_mat   | 0.77 | 0.77  |       |
| mmu-miR-24-000402         | 0.77 | 0.34  | 0.93  |
| mmu-miR-1969-121131_mat   | 0.76 | 0.96  |       |
| mmu-miR-320-002277        | 0.74 | 0.90  | 4.38  |
| mmu-miR-872-002264        | 0.73 | 1.06  |       |
| rno-miR-673-002054        | 0.73 | 0.73  |       |
| mmu-miR-877#-002548       | 0.72 | 0.95  | 2.37  |
| hsa-miR-200c-000505       | 0.72 | 0.03  |       |
| rno-miR-190b-002048       | 0.68 | 0.78  |       |
| mmu-miR-223-002295        | 0.67 | 0.88  |       |
| mmu-miR-301a-000528       | 0.67 | 0.08  |       |
| mmu-miR-152-000475        | 0.66 | 0.70  |       |
| mmu-miR-465C-5P-002654    | 0.65 | 0.53  |       |
| mmu-miR-24-2#-002494      | 0.65 | 0.65  | 75.38 |
| mmu-miR-467b-001684       | 0.64 | 0.64  |       |
| mmu-miR-92a-000430        | 0.64 | 0.43  | 0.01  |
| hsa-miR-140-3p-002234     | 0.63 | 0.72  |       |
| mmu-miR-155-002571        | 0.63 | 0.72  |       |
| mmu-miR-467F-002886       | 0.61 | 21.32 |       |

|                           |      |      |       |
|---------------------------|------|------|-------|
| mmu-miR-188-3p-002106     | 0.61 | 0.61 |       |
| rno-miR-664-001323        | 0.59 | 0.10 | 8.44  |
| mmu-miR-574-3p-002349     | 0.58 | 0.04 | 44.03 |
| mmu-miR-1961-197391_mat   | 0.57 | 0.57 |       |
| mmu-miR-1274a-121150_mat  | 0.57 | 0.70 |       |
| mmu-miR-106a-002459       | 0.56 | 0.84 |       |
| hsa-miR-378-000567        | 0.55 | 0.62 | 1.64  |
| mmu-miR-181A-2#-002687    | 0.55 | 0.55 |       |
| ath-miR159a-000338        | 0.55 | 0.55 |       |
| mmu-miR-29a-002112        | 0.53 | 1.70 |       |
| mmu-miR-150-000473        | 0.51 | 0.69 |       |
| mmu-miR-25-000403         | 0.50 | 1.29 |       |
| mmu-miR-451-001141        | 0.49 | 0.81 |       |
| mmu-miR-470#-002589       | 0.49 | 0.92 |       |
| mmu-miR-2138-241080_mat   | 0.49 | 0.15 |       |
| mmu-miR-29c-000587        | 0.45 | 0.70 |       |
| mmu-miR-1901-121183_mat   | 0.43 | 0.49 |       |
| mmu-miR-328-000543        | 0.43 | 0.48 | 2.36  |
| hsa-miR-143-000466        | 0.41 | 0.89 |       |
| mmu-miR-466b-3-3p-002500  | 0.41 | 0.91 |       |
| mmu-miR-1982.2-121154_mat | 0.39 | 2.17 |       |
| mmu-miR-133a-002246       | 0.38 | 0.44 | 0.03  |
| mmu-miR-467a-001826       | 0.38 | 2.13 |       |
| mmu-miR-146b-001097       | 0.35 | 0.42 |       |
| mmu-miR-19a-000395        | 0.33 | 0.31 |       |
| mmu-miR-126-3p-002228     | 0.33 | 0.40 |       |
| mmu-miR-743a-002469       | 0.29 | 0.29 |       |
| mmu-miR-29b-000413        | 0.27 | 0.27 |       |
| rno-miR-1-002064          | 0.25 | 0.19 | 2.44  |
| mmu-miR-126-5p-000451     | 0.25 | 1.62 |       |
| mmu-miR-692-001679        | 0.18 | 1.00 |       |
| mmu-miR-429-001077        | 0.17 | 0.17 |       |
| mmu-miR-1939-121180_mat   | 0.15 | 0.45 |       |
| mmu-miR-450b-5p-001962    | 0.14 | 0.56 |       |
| mmu-miR-133b-002247       | 0.13 | 0.13 |       |
| mmu-miR-93-001090         | 0.12 | 0.01 |       |
| mmu-miR-465a-5p-001082    | 0.12 | 0.22 |       |
| mmu-miR-197-000497        | 0.10 | 0.10 |       |
| mmu-miR-504-002084        | 0.09 | 0.04 |       |
| mmu-miR-215-001200        | 0.09 | 0.52 |       |
| mmu-miR-125b-5p-000449    | 0.09 | 0.05 |       |
| rno-miR-878-002070        | 0.08 | 0.08 |       |
| mmu-let-7d-002283         | 0.06 | 0.06 |       |
| mmu-miR-218-000521        | 0.05 | 0.05 |       |
| hsa-miR-214-000517        | 0.05 | 0.05 | 11.40 |
| mmu-miR-188-5p-002320     | 0.05 | 0.15 | 1.18  |

|                         |      |      |       |
|-------------------------|------|------|-------|
| mmu-miR-331-3p-000545   | 0.05 | 0.05 |       |
| mmu-miR-130a-000454     | 0.04 | 0.04 |       |
| hsa-miR-30e-3p-000422   | 0.04 | 0.04 |       |
| mmu-miR-1-002222        | 0.03 | 0.16 |       |
| hsa-miR-30a-3p-000416   | 0.03 | 0.03 | 48.46 |
| mmu-miR-2182-241119_mat | 0.02 | 0.18 |       |
| mmu-miR-326-001061      | 0.01 | 0.51 | 0.88  |

**Supplementary Table 1 Changes in miRNAs patterns in exosomes from mice or BA after activation, related to Figure 2**

Serum exosomal miRNAs up- or down-regulated more than 2-fold in either CL316,243-treated (CL) or in cold-exposed mice (cold) (versus wild type controls) and exosomal miRNAs up- or down-regulated more than in cAMP-treated BA (versus untreated BA controls). miRNAs up-regulated are indicated in red; down-regulated in blue; undetected miRNAs are listed in black. Investigated candidates are highlighted in white.

|            | Serum-exo<br><i>in vivo</i> |        | BA-exo<br><i>in vitro</i> |
|------------|-----------------------------|--------|---------------------------|
|            | CL-316.243                  | Cold   | cAMP                      |
| miR-34c*   | 40.101                      | 4.421  | 8.722                     |
| miR-339-3p | 10.419                      | 1.000  | 27.631                    |
| miR-149    | 1.000                       | 35.871 | 4.970                     |
| miR-93*    | 0.667                       | 31.295 | 3.940                     |
| miR-409-3p | 0.396                       | 0.844  | 0.326                     |
| miR-92a    | 0.427                       | 0.637  | 0.014                     |
| miR-133a   | 0.441                       | 0.383  | 0.032                     |

**Supplementary Table 2 Expression of the seven deregulated miRNA candidates in mice, related to Figure 2**

Seven miRNA candidates found in serum of mice with active BAT (CL-316.243 or cold) and in brown adipocytes treated with cAMP respective to wild type mice and untreated brown adipocytes. Given are Fold Changes (FC) of Relative Quantitation (RQ) compared to wild type mice and untreated brown adipocytes.

| ID | AGE | BMI   | SEX | Fat   | Glucose Uptake Rate | BAT SUVmax | Pre-BSm | Post-BSm | $\Delta$ Bsm | Predicted $\Delta$ Bsm | Pre-LgmiR92 | Post-LgmiR92 | $\Delta$ LgmiR92 | Acute cold sample |
|----|-----|-------|-----|-------|---------------------|------------|---------|----------|--------------|------------------------|-------------|--------------|------------------|-------------------|
| 2  | 20  | 19.90 | 0   | 15.80 | 0.00                | 0.60       | 0.37    | 1.96     | 1.59         | 0.45                   | 1.60        | 1.08         | -0.51            |                   |
| 4  | 25  | 23.40 | 1   | 12.60 | 10.22               | 22.63      | 2.92    | 2.53     | -0.38        | -0.11                  | 1.55        | 1.68         | 0.13             | x                 |
| 5  | 22  | 20.30 | 0   | 14.80 | 5.40                | 8.86       | 2.25    | 2.01     | -0.24        | 0.24                   | 1.05        | 0.78         | -0.27            | x                 |
| 6  | 24  | 21.70 | 0   | 25.70 | 4.92                | 20.19      | 2.69    | 3.11     | 0.42         | -0.22                  | 1.02        | 1.27         | 0.25             | x                 |
| 7  | 20  | 21.90 | 0   | 22.10 | 1.93                | 4.97       | 1.91    | 2.75     | 0.84         | 0.47                   | 1.44        | 0.91         | -0.53            | x                 |
| 8  | 19  | 19.90 | 1   | 12.50 | 10.44               | 17.68      | 2.87    | 2.95     | 0.09         | 0.03                   | 0.97        | 0.94         | -0.03            |                   |
| 10 | 23  | 20.80 | 0   | 12.80 | 5.67                | 21.04      | 2.96    | 3.85     | 0.89         | -0.01                  | 0.98        | 1.00         | 0.02             | x                 |
| 11 | 21  | 18.40 | 1   | 13.40 | 10.67               | 22.37      | 2.95    | 2.55     | -0.39        | -0.02                  | 0.47        | 0.49         | 0.02             | x                 |
| 13 | 25  | 25.70 | 1   | 12.50 | 5.46                | 5.45       | 2.02    | 2.46     | 0.44         | 0.38                   | 1.52        | 1.09         | -0.43            |                   |
| 14 | 18  | 20.40 | 1   | 8.40  | 11.00               | 23.40      | 2.87    | 3.46     | 0.59         | 0.17                   | 1.20        | 1.00         | -0.20            |                   |

**Supplementary Table 3 Cohort 1 subject characteristics for participants in the 10 day cold acclimation study, related to Figure 3**

Shown are age, BMI in  $\text{kg m}^{-2}$ , sex (0, female; 1, male), Fat in kg, Glucose Uptake Rate in  $\mu\text{mol } 100\text{g}^{-1} \text{ min}^{-1}$ , BAT SUVmax, BAT SUVmean before (Pre-BSm) and after cold acclimation (Post-BSm), delta BAT SUVmean ( $\Delta$ Bsm), the predicted BAT SUVmean (Predicted  $\Delta$ Bsm; Fig. 3d),  $\text{Log}_{10}$  miR-92a (Pre-LgmiR92 or Post-LgmiR92) and  $\Delta\text{Log}_{10}$  miR-92a, respectively. Additionally it is listed whether an acute cold sample was taken utilized for Supplemental Fig. 3e.

| ID | AGE | BMI   | SEX | Fat   | GlucoseUptakeRate | BAT SUVmean | BAT SUVmax | Log <sub>10</sub> miR-92a | Acute cold sample |
|----|-----|-------|-----|-------|-------------------|-------------|------------|---------------------------|-------------------|
| 1  | 19  | 23.82 | 0   | 22.28 | 7.09              | 2.83        | 12.70      | 4.57                      |                   |
| 2  | 20  | 21.76 | 1   | 7.54  | 12.23             | 3.26        | 25.04      | 13.96                     | x                 |
| 3  | 21  | 21.89 | 1   | 10.71 | 7.56              | 2.72        | 11.03      | 18.25                     |                   |
| 4  | 20  | 21.43 | 1   | 11.46 | 11.01             | 3.19        | 19.76      | 8.11                      | x                 |
| 5  | 23  | 20.85 | 0   | 15.74 | 6.61              | 2.70        | 16.09      | 78.84                     | x                 |
| 6  | 20  | 18.54 | 1   | 6.09  | 9.57              | 2.98        | 17.59      | 8.55                      | x                 |
| 7  | 23  | 19.62 | 0   | 19.93 | 3.01              | 2.01        | 5.16       | 8.35                      | x                 |
| 8  | 21  | 20.18 | 0   | 15.33 | 0.00              | 0.00        | 0.61       | 77.04                     |                   |
| 9  | 19  | 22.29 | 0   | 17.94 | 4.43              | 2.05        | 6.71       | 40.39                     | x                 |
| 10 | 24  | 21.20 | 1   | 13.23 | 0.00              | 1.70        | 2.16       | 41.51                     | x                 |
| 11 | 26  | 21.25 | 1   | 10.98 | 5.32              | 2.31        | 7.47       | 145.28                    | x                 |
| 12 | 19  | 22.30 | 0   | 19.04 | 3.76              | 2.30        | 7.33       | 103.01                    | x                 |

**Supplementary Table 4 Cohort 1 subject characteristics for 12 lean participants in the thermoneutral study, related to Figure 3**

Shown are age, BMI in kg m<sup>2</sup>, sex (0, female; 1, male), Fat in kg, Glucose Uptake Rate in  $\mu\text{mol } 100\text{g}^{-1} \text{ min}^{-1}$ , BAT SUVmean, BAT SUVmax, Log<sub>10</sub> miR-92a. Additionally it is listed whether an acute cold sample was taken utilized for Supplemental Fig. 3e

| ID | AGE | BMI  | SEX | Fat  | GlucoseUptakeRate | Log <sub>10</sub> miR-92a |
|----|-----|------|-----|------|-------------------|---------------------------|
| 1  | 47  | 24.7 | 0   | 35.1 | 17.1              | 1.67                      |
| 2  | 30  | 26.6 | 1   | 22.6 | 1                 | 1.93                      |
| 3  | 46  | 24.5 | 0   | 34.6 | 2.2               | 2.20                      |
| 4  | 21  | 18.9 | 0   | 22.1 | 10.7              | 1.93                      |
| 5  | 38  | 20.5 | 0   | 28   | 4.9               | 2.28                      |
| 6  | 40  | 24.2 | 0   | 32.9 | 3.9               | 1.49                      |
| 7  | 48  | 20.4 | 1   | 19.3 | 0.9               | 2.11                      |
| 8  | 50  | 22.7 | 0   | 33.3 | 1.4               | 2.24                      |
| 9  | 51  | 23.5 | 0   | 34.5 | 3.7               | 1.84                      |
| 10 | 44  | 23.6 | 0   | 33   | 6.3               | 2.22                      |
| 11 | 28  | 24.2 | 0   | -    | 32.7              | 1.28                      |
| 12 | 35  | -    | 1   | -    | 8.7               | 1.56                      |
| 13 | 25  | 23   | 1   | 16.6 | 7.9               | 1.49                      |
| 14 | 25  | 24.7 | 0   | 25.8 | 21                | 1.22                      |
| 15 | 24  | 20.3 | 0   | 25.8 | 22.8              | 1.80                      |
| 16 | 31  | 25.1 | 0   | 36.1 | 26.3              | 1.11                      |
| 17 | 25  | 25.1 | 1   | 20.1 | 9.5               | 2.53                      |
| 18 | 39  | 28.9 | 1   | 18.6 | 23.1              | 1.60                      |
| 19 | 43  | 23.4 | 0   | 34   | 8.4               | 2.60                      |

**Supplementary Table 5 Cohort 2 subject characteristics for 19 lean participants in the second thermoneutral study, related to Figure 3**

Shown are age, BMI in kg m<sup>-2</sup>, sex (0, female; 1, male), Fat in kg, Glucose Uptake Rate in  $\mu\text{mol } 100\text{g}^{-1} \text{ min}^{-1}$ , and Log<sub>10</sub> miR-92a.

| Correlation Cohort1        |                 |       |       |         |         |                   |             |            |                           |                            |
|----------------------------|-----------------|-------|-------|---------|---------|-------------------|-------------|------------|---------------------------|----------------------------|
|                            |                 | AGE   | BMI   | Sex     | Fat     | GlucoseUptakeRate | BAT SUVmean | BAT SUVmax | Log <sub>10</sub> miR-92a | Log <sub>10</sub> miR-133a |
| AGE                        | Pearson         | 1     | .247  | .139    | .026    | -.220             | -.056       | -.110      | .292                      | .159                       |
|                            | t-test (2-tail) |       | .268  | .538    | .909    | .326              | .806        | .626       | .188                      | .479                       |
|                            | N               | 22    | 22    | 22      | 22      | 22                | 22          | 22         | 22                        | 22                         |
| BMI                        | Pearson         | .247  | 1     | .164    | .235    | -.041             | .065        | -.118      | .270                      | .157                       |
|                            | t-test (2-tail) | .268  |       | .465    | .294    | .856              | .773        | .600       | .224                      | .485                       |
|                            | N               | 22    | 22    | 22      | 22      | 22                | 22          | 22         | 22                        | 22                         |
| Sex                        | Pearson         | .139  | .164  | 1       | -.749** | .509*             | .369        | .294       | .035                      | .259                       |
|                            | t-test (2-tail) | .538  | .465  |         | .000    | .016              | .091        | .184       | .876                      | .245                       |
|                            | N               | 22    | 22    | 22      | 22      | 22                | 22          | 22         | 22                        | 22                         |
| Fat                        | Pearson         | .026  | .235  | -.749** | 1       | -.536*            | -.292       | -.353      | .012                      | -.306                      |
|                            | t-test (2-tail) | .909  | .294  | .000    |         | .010              | .187        | .107       | .959                      | .166                       |
|                            | N               | 22    | 22    | 22      | 22      | 22                | 22          | 22         | 22                        | 22                         |
| GlucoseUptakeRate          | Pearson         | -.220 | -.041 | .509*   | -.536*  | 1                 | .863**      | .883**     | -.505*                    | -.112                      |
|                            | t-test (2-tail) | .326  | .856  | .016    | .010    |                   | .000        | .000       | .016                      | .618                       |
|                            | N               | 22    | 22    | 22      | 22      | 22                | 22          | 22         | 22                        | 22                         |
| BAT SUVmean                | Pearson         | -.056 | .065  | .369    | -.292   | .863**            | 1           | .858**     | -.510*                    | -.315                      |
|                            | t-test (2-tail) | .806  | .773  | .091    | .187    | .000              |             | .000       | .015                      | .153                       |
|                            | N               | 22    | 22    | 22      | 22      | 22                | 22          | 22         | 22                        | 22                         |
| BAT SUVmax                 | Pearson         | -.110 | -.118 | .294    | -.353   | .883**            | .858**      | 1          | -.528*                    | -.114                      |
|                            | t-test (2-tail) | .626  | .600  | .184    | .107    | .000              | .000        |            | .012                      | .613                       |
|                            | N               | 22    | 22    | 22      | 22      | 22                | 22          | 22         | 22                        | 22                         |
| Log <sub>10</sub> miR-92a  | Pearson         | .292  | .270  | .035    | .012    | -.505*            | -.510*      | -.528*     | 1                         | .432*                      |
|                            | t-test (2-tail) | .188  | .224  | .876    | .959    | .016              | .015        | .012       |                           | .045                       |
|                            | N               | 22    | 22    | 22      | 22      | 22                | 22          | 22         | 22                        | 22                         |
| Log <sub>10</sub> miR-133a | Pearson         | .159  | .157  | .259    | -.306   | -.112             | -.315       | -.114      | .432*                     | 1                          |
|                            | t-test (2-tail) | .479  | .485  | .245    | .166    | .618              | .153        | .613       | .045                      |                            |
|                            | N               | 22    | 22    | 22      | 22      | 22                | 22          | 22         | 22                        | 22                         |

**Supplementary Table 6 Pearson Correlation for 22 lean participants of the thermoneutral study, related to Figure 3**

Shown are age, BMI in kg m<sup>2</sup>, sex (0, female; 1, male), Fat in kg, Glucose Uptake Rate in μmol 100g<sup>-1</sup> min<sup>-1</sup>, BAT SUVmean, BAT SUVmax, Log<sub>10</sub> miR-92a and the respective Log<sub>10</sub> miR-133a. Values are Pearson correlation coefficients ( $P^* \leq 0.05$ ,  $**P \leq 0.01$ ).



| Correlation Cohort2       |                 |       |       |         |         |                   |                           |
|---------------------------|-----------------|-------|-------|---------|---------|-------------------|---------------------------|
|                           |                 | AGE   | BMI   | Sex     | Fat     | GlucoseUptakeRate | Log <sub>10</sub> miR-92a |
| AGE                       | Pearson         | 1     | .089  | -.186   | .560*   | -.479             | .354                      |
|                           | t-test (2-tail) |       | .727  | .447    | .019    | .038              | .137                      |
|                           | N               | 19    | 18    | 19      | 17      | 19                | 19                        |
| BMI                       | Pearson         | .089  | 1     | .324    | .042    | .242              | -.271                     |
|                           | t-test (2-tail) | .727  |       | .190    | .873    | .333              | .276                      |
|                           | N               | 18    | 18    | 18      | 17      | 18                | 18                        |
| Sex                       | Pearson         | -.186 | .324  | 1       | -.814** | -.192             | .036                      |
|                           | t-test (2-tail) | .447  | .190  |         | .000    | .430              | .883                      |
|                           | N               | 19    | 18    | 19      | 17      | 19                | 19                        |
| Fat                       | Pearson         | .560* | .042  | -.814** | 1       | -.040             | .026                      |
|                           | t-test (2-tail) | .019  | .873  | .000    |         | .880              | .921                      |
|                           | N               | 17    | 17    | 17      | 17      | 17                | 17                        |
| GlucoseUptakeRate         | Pearson         | -.479 | .242  | -.192   | -.040   | 1                 | -.630**                   |
|                           | t-test (2-tail) | .038  | .333  | .430    | .880    |                   | .004                      |
|                           | N               | 19    | 18    | 19      | 17      | 19                | 19                        |
| Log <sub>10</sub> miR-92a | Pearson         | .354  | -.271 | .036    | .026    | -.630**           | 1                         |
|                           | t-test (2-tail) | .137  | .276  | .883    | .921    | .004              |                           |
|                           | N               | 19    | 18    | 19      | 17      | 19                | 19                        |

**Supplementary Table 7 Pearson Correlation for 19 lean participants of a second thermoneutral study, related to Figure 3**

Pearson Correlation for 19 lean participants of a second thermoneutral study. Shown are age, BMI in kg m<sup>2</sup>, sex (0, female; 1, male), Fat in kg, C-reactive Protein in mgL<sup>-1</sup>, Glucose Uptake Rate in μmol 100g<sup>-1</sup> min<sup>-1</sup> and Log<sub>10</sub> miR-92a. Values are Pearson correlation coefficients ( $P \leq 0.05$ ,  $**P \leq 0.01$ ).