FIGURE S1 **Transgene expression in TgβARKct and TgGRK2 mice.** *A,* Heart and eWAT lysate were subjected to immunoprecipitation using a GRK2 antibody to detect βARKct. Lysate from AC-16 cells infected with AdβARKct was used as a control. IgG heavy chain (HC) and light chain (LC) are marked. *B,* Representative Western blot showing Tg GRK2 overexpression is limited to TgGRK2 hearts with no ectopic expression in eWAT samples.

FIGURE S2 **Body weight measurements of high fat diet fed mice**. *A,* Body weight of TgβARKct and NLC mice fed control or HFD for 6 weeks. n=7-16 per group; *, $P<0.05$; **, $P<0.01$. *B,* Body weight of TgGRK2 and NLC mice fed CD or HFD for 6 weeks. n=7-11 per group; **, $P<0.01$.

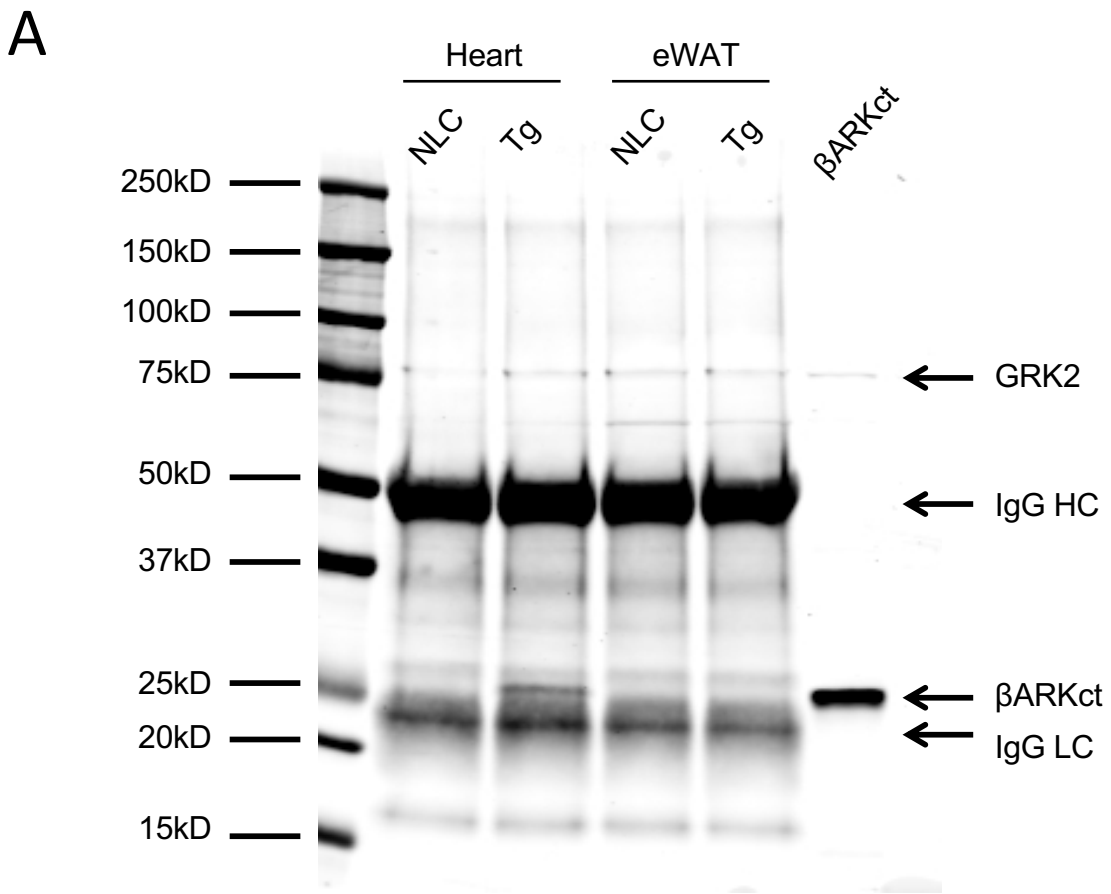
FIGURE S3 **Respiration and physical activity in TgβARKct and NLC mice**. Mice were analyzed in metabolic chambers for 10 days. Mice were fed a standard control diet (CD) for the first 5 days, then switched to high fat diet (HFD) for the last 5 days. *A,* Averaged oxygen consumption per hour, normalized to body weight in animals fed CD, over a 12 hr light/dark cycle. *B*, Averaged oxygen consumption per hr, normalized to body weight in animals fed a HFD, over a 12 hr light/dark cycle. *C,* Averaged carbon dioxide production per hr, normalized to body weight in animals fed CD, over a 12 hr light/dark cycle. *D*, Averaged carbon dioxide production per hr, normalized to body weight in animals fed HFD, over a 12 hr light/dark cycle. *E,* Respiratory exchange ratio. Shaded and unshaded areas represent the dark and light cycles, respectively. Arrow indicates the point at which food was switched from control to high fat chow. *F,* Physical activity measured via beam breaks over a 12 hr light/dark cycle. n=5 mice per group.

FIGURE S4 **Respiration and physical activity in TgGRK2 and NLC mice**. Mice were analyzed in metabolic chambers for 10 days. Mice were fed a standard control diet (CD) for the first 5 days, then switched to high fat diet (HFD) for the last 5 days. *A,* Averaged oxygen consumption per hr, normalized to body weight in animals fed CD, over a 12 hr light/dark cycle. *B*, Averaged oxygen consumption per hr, normalized to body weight in animals fed HFD, over a 12 hr light/dark cycle. *C,* Averaged carbon dioxide production per hr, normalized to body weight in animals fed CD, over a 12 hr light/dark cycle. *D*, Averaged carbon dioxide production per hr, normalized to body weight in animals fed HFD, over a 12 hr light/dark cycle. *E,* Respiratory exchange ratio. Shaded and unshaded areas represent the dark and light cycles, respectively.

Arrow indicates the point at which food was switched from control to high fat chow. *F,* Physical activity measured via beam breaks over a 12 hr light/dark cycle. n=5 mice per group.

FIGURE S5 **Validation of serum BCAA metabolite levels following HFD.** Serum samples from mice following 4 weeks of HFD were analyzed for α-hydroxyisovalerate (HIVA) and 2-hydroxy-3-methylvalerate (HMVA) levels using HILIC/UPLC-MS/MS with negative ion mode ESI. *, $P<0.05$; ***, $P<0.001$

Figure S1


A
Heart
eWAT
NLC
Tg
NLC
Tg
βARKct
250kD
150kD
100kD
75kD
50kD
37kD
25kD
20kD
15kD
GRK2
IgG HC
βARKct
IgG LC

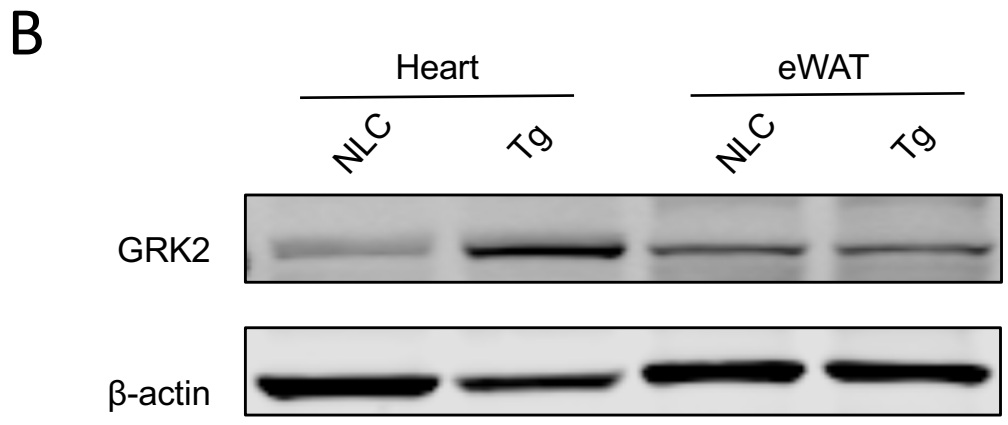
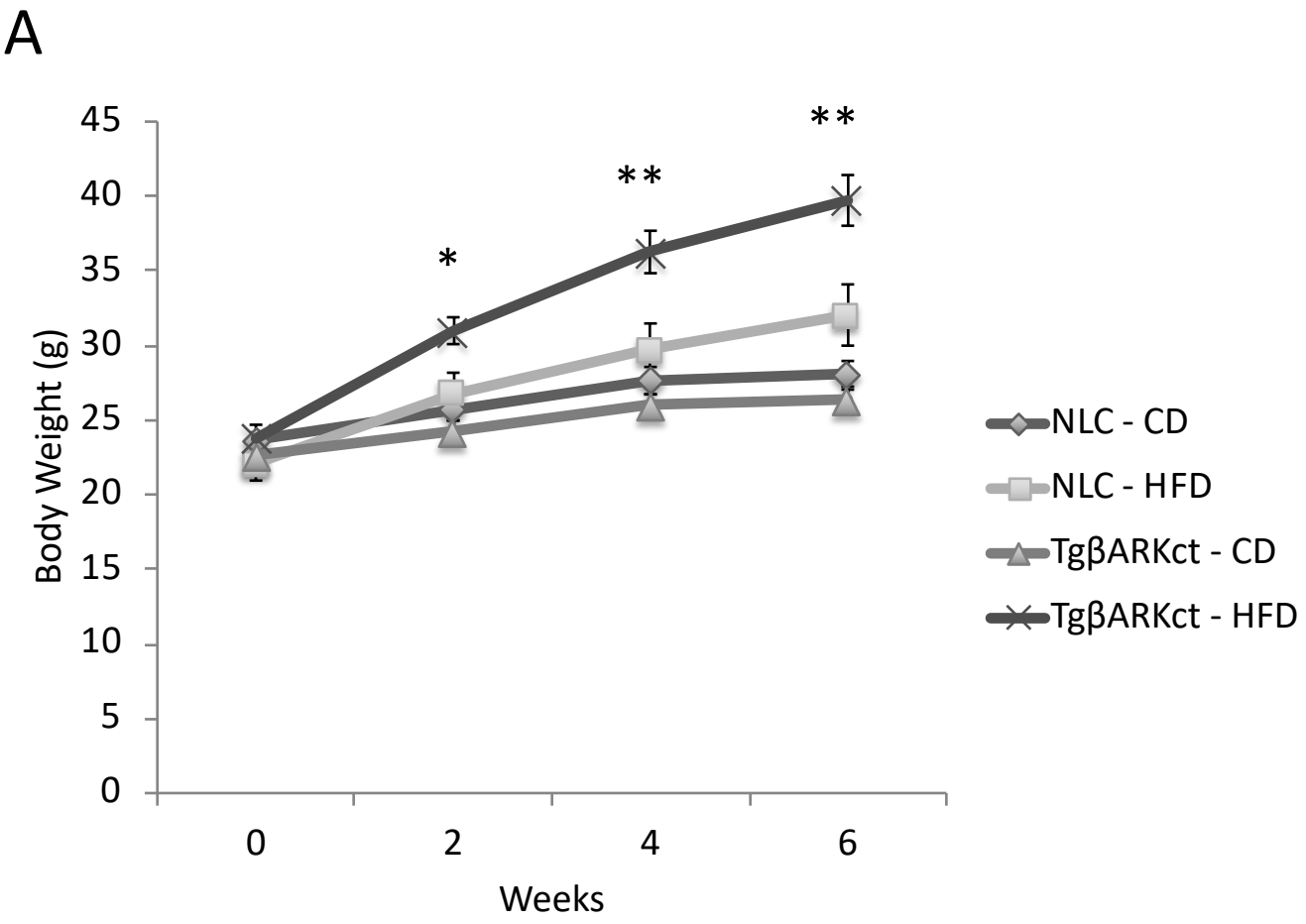

B
Heart
eWAT
NLC
Tg
NLC
Tg
GRK2
β-actin

Figure S2


A
45
40
35
30
25
20
15
10
5
0
Body Weight (g)
0
2
4
6
Weeks
*
**
**
NLC - CD
NLC - HFD
TgβARKct - CD
TgβARKct - HFD

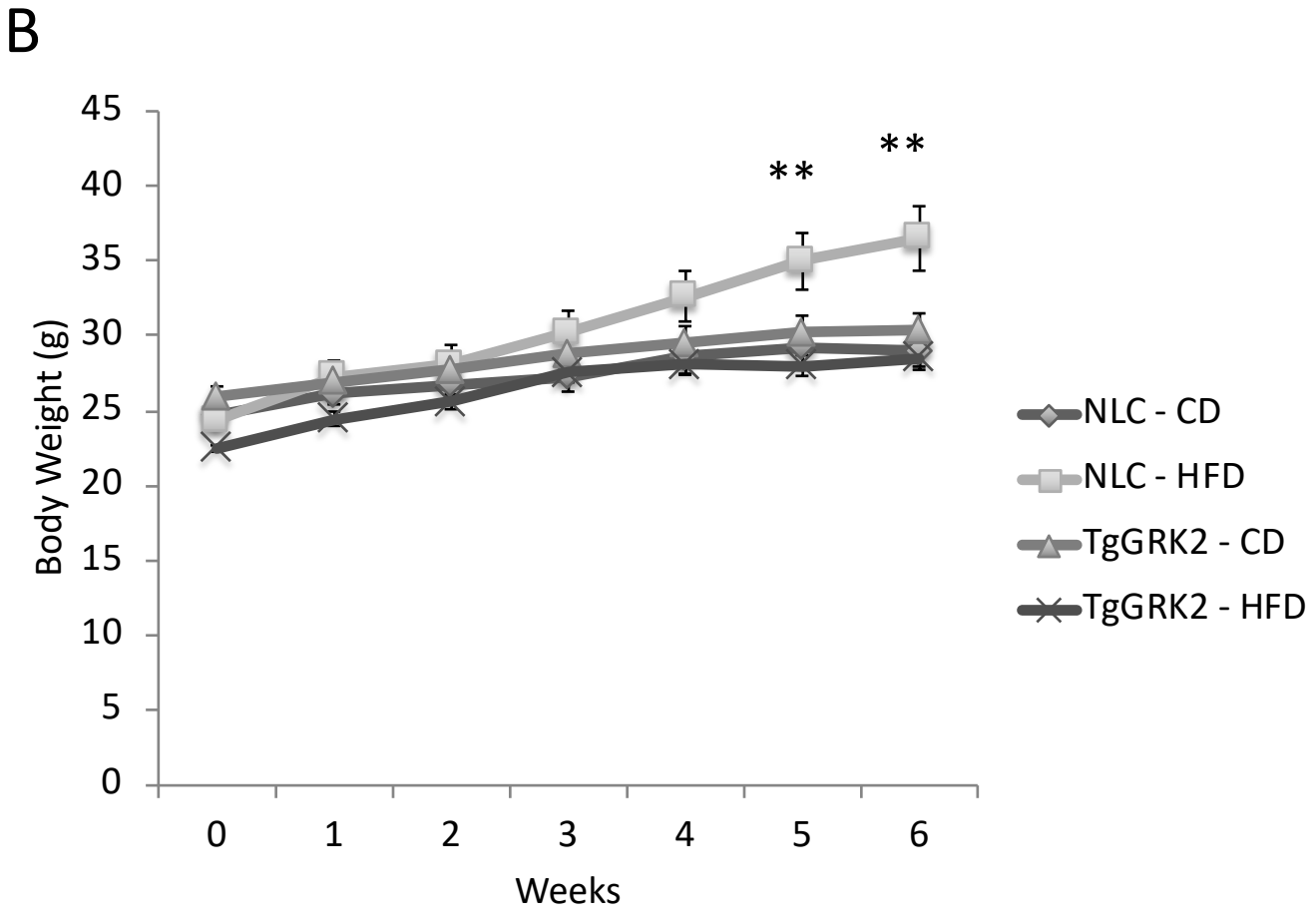

B
45
40
35
30
25
20
15
10
5
0
Body Weight (g)
0
1
2
3
4
5
6
Weeks
**
**
NLC - CD
NLC - HFD
TgGRK2 - CD
TgGRK2 - HFD

Figure S3

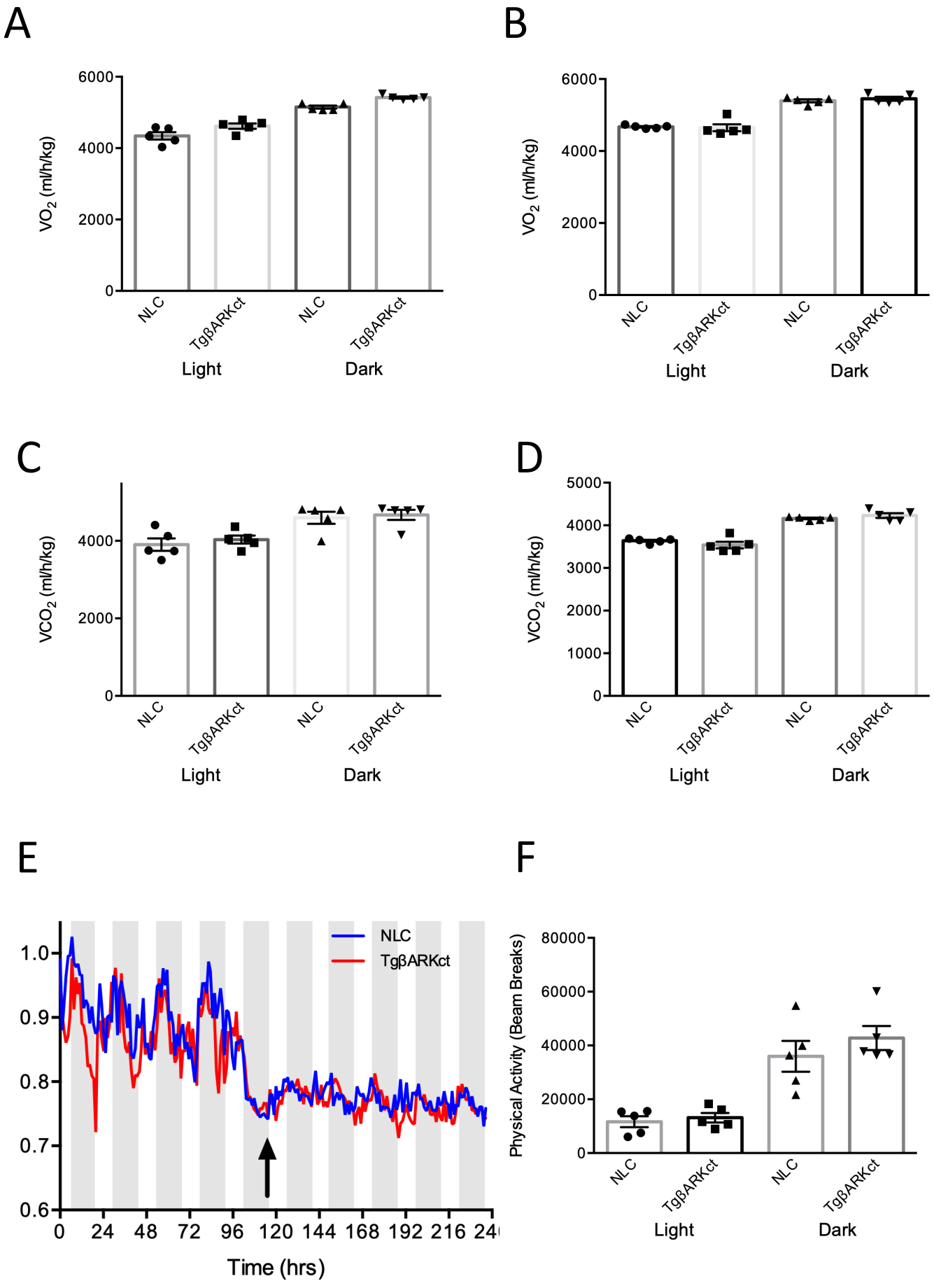

A
B
C
D
E
F
VO_2 (ml/h/kg)
VCO_2 (ml/h/kg)
NLC
TgβARKct
Light
Dark
Respiratory Exchange Ratio
Time (hrs)
Physical Activity (Beam Breaks)

Figure S4

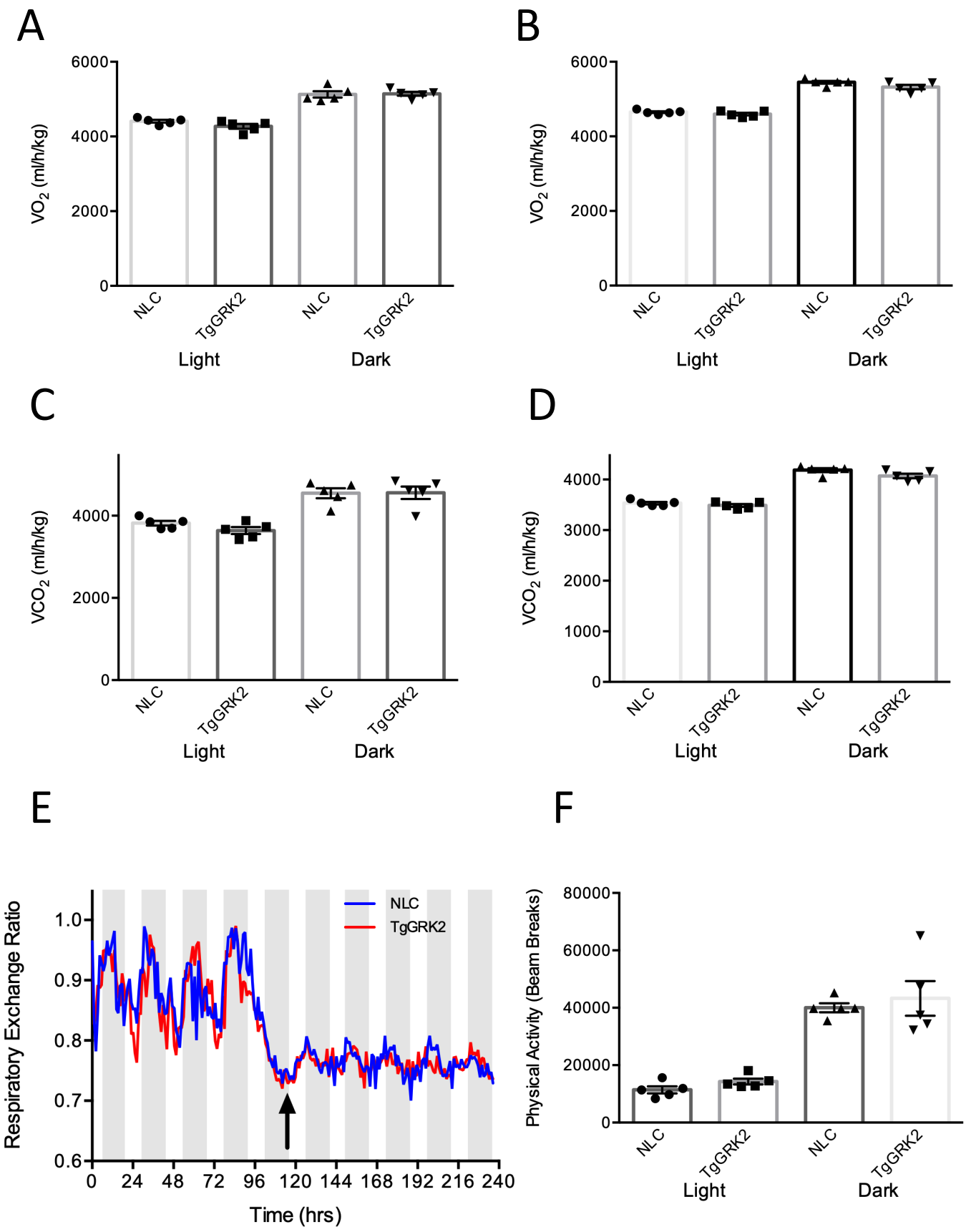
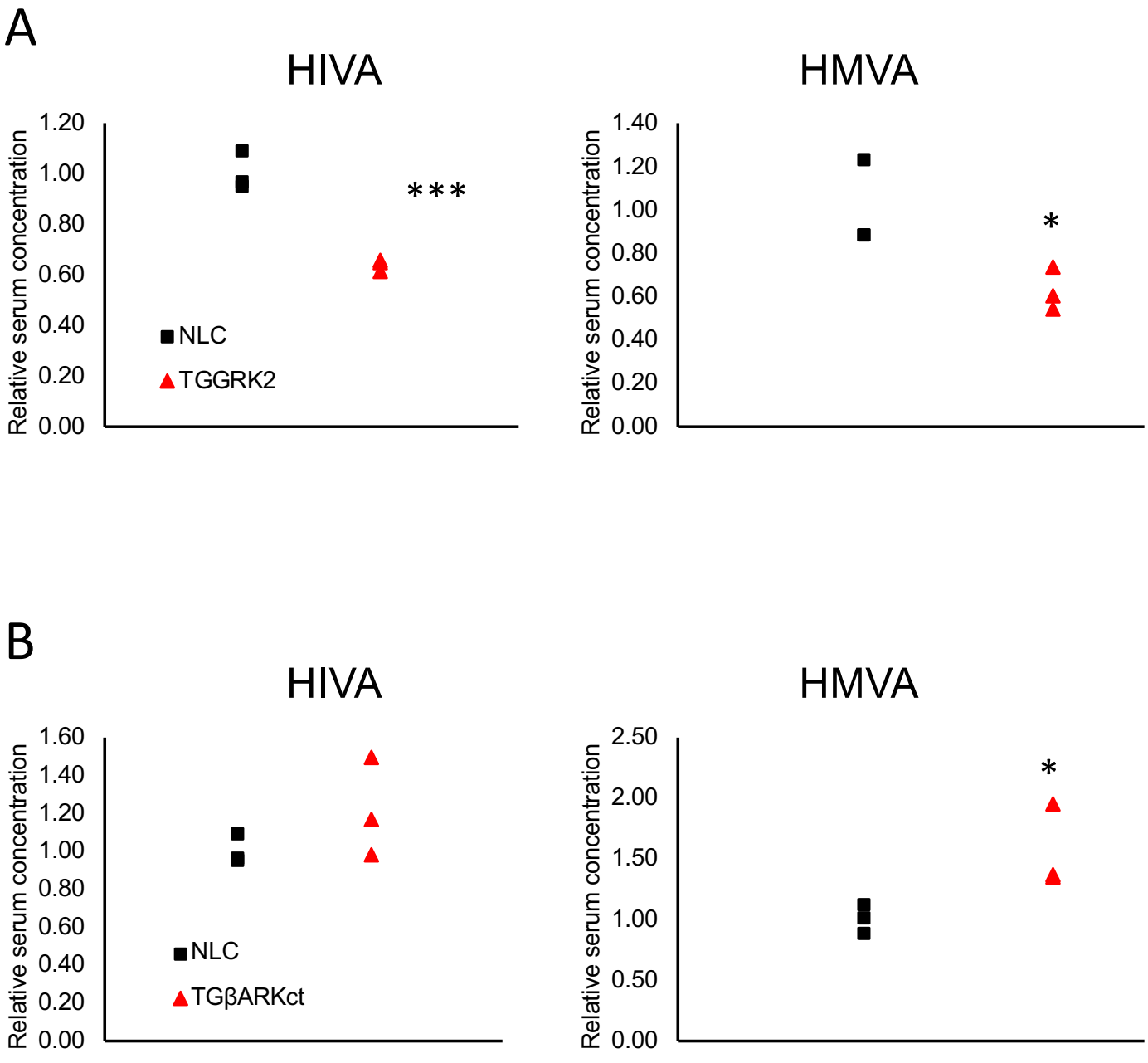

A
B
C
D
E
F
VO_2 (ml/h/kg)
VCO_2 (ml/h/kg)
NLC
TgGRK2
Light
Dark
Respiratory Exchange Ratio
Time (hrs)
Physical Activity (Beam Breaks)

Figure S5


A
HIVA
Relative serum concentration
1.20
1.00
0.80
0.60
0.40
0.20
0.00
***
NLC
TGGRK2
HMVA
Relative serum concentration
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
*
B
HIVA
Relative serum concentration
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
NLC
TGβARKct
HMVA
Relative serum concentration
2.50
2.00
1.50
1.00
0.50
0.00
*