Supplemental Experimental Procedures

RT-PCR and detection of mRNA expression of *ghsr1a* and *drd2* in mouse brain. Tissue extractions for analysis of gene expression were carried out on adult 3 month old mice. Mice were killed by decapitation after a brief exposure to carbon dioxide brains were removed and immediately dissected using a coronal brain matrix. All tissue samples were immediately homogenized in TRIzol (Invitrogen, Carlsbad, CA) using an MP-Fastprep 24 tissue homogenizator (MP Biochemicals, Irvine, CA). Total RNA was isolated from tissue homogenates by use of RNeasy Midi kit (Qiagen, Valencia, CA). Template cDNA was prepared by RT from 400 ng of total RNA using SuperScript III first-strand synthesis system (Invitrogen), according to manufacturer's instructions. The RT products were amplified by PCR using following intron flanking primers: *Ghsr*Fw753: 5' CAGGGACCAGAACCACAAAC; *Ghsr*Rev942: 5' AGCGCTGAGGTAGAAGAGGAC; *Drd2*Fw888: 5'CCCCATCCCTCCCAGTCACC; Drd2Rev1173: 5'GAAGAAGGGCAGCCAGCAGATG; GapdhFw: 5' CTCACGGCAAATTCAACGG; GapdhRev: 5' CTTTCCAGAGGGGCCATCCA. PCR products were separated on 2% agarose gels and visualized by ethidium bromide.

Immunofluorescence microscopy of mouse brain sections. Immunofluorescence was carried out on adult male *ghsr-IRES-tauGFP* mice as described previously (Jiang et al., 2006). Brains were quickly removed as described above, snap frozen and stored at -80°C. Frozen brains were embedded with Tissue-Tek (Sakura Finetek) and cut into 20 μm coronal sections using Leica CM1950 cryostat (Leica Microsytems). Brain sections were fixed in 4% paraformaldehyde for 30 min at room temperature, rinsed in PBS, permeabilized with 0.25% Triton X-100 in PBS for

30 min at room temperature and washed with PBS. After blocking with 1% BSA/ PBS for 1 hour at room temperature, sections were incubated with mouse anti-DRD2 monoclonal antibody (1:200 dilution, Santa Cruz Biotechnology, Santa Cruz, CA,) and rabbit anti-GFP antibody (1:1000 dilutions, Invitrogen) in a humidified chamber at 4°C overnight in 0.1% BSA/PBS . Sections were then washed with 0.1% BSA/PBS and incubated with secondary goat anti-mouse AlexaFluor 647 (Invitrogen) and goat anti-rabbit AlexaFluor 488 (Invitrogen) for 2 hours at room temperature. After washes, slides were mounted with Vectashield (Vector Laboratories, Burlingame, CA) and laser scanning confocal microscopy was performed using Olympus FluoView 1000.

Cell culture, plasmid and siRNA transfections. HEK293 (ATCC number: CRL-1573) and neuronal SH-SY5Y (ATCC number: CRL-2266) cells were grown routinely in DMEM/F12 supplemented with 10 % fetal bovine serum and 100 μg/ml of penicillin/streptomycin in a humidified atmosphere at 37°C and 95% air/5% CO_2. HEK293 cells stably expressing aequorin (HEK-AEQ) were maintained in above media containing 500 μg/ml Geneticin (Invitrogen). Mouse hypothalamic tissue of embryonic day 18 mouse was purchased from BrainBits (Springfield, IL), primary neurons were prepared and the $[Ca^{2+}]_i$ mobilization assay performed after cultivating neurons in NbActiv4 neuronal culture medium (BrainBits). Transient transfections were carried out using Lipofectamine 2000 (Invitrogen). 10^6 HEK-AEQ cells were transfected with 0.1 μg of the GHSR1a and 0.5 μg of DRD2 cDNA. The stable SH-SY5Y cell line expressing GHSR1a (SH-GHSR1a) was established by electroporating HA-tagged GHSR1a into SH-SY5Y under Geneticin selection (400 μg/ml). The clones were tested for GHSR1a expression by immunofluorescence cell sorting and microscopy against the HA-tag, and for function by measuring ghrelin-induced inositol phosphate production. The human $G\alpha_q$ and

control siRNA oligos were obtained from Santa Cruz Biotechnology. Cells were transfected in 6-well plates with 100 pmol of siRNA using Lipofectamine 2000. Assays were performed 48 h after siRNA transfection.

Ca^{2+} mobilization assays. The aequorin bioluminescence assay was carried out as described previously (Feighner et al., 1998; Howard et al., 1996). Briefly, twenty-four hours after transfection of HEK-AEQ cells in 6-well plates, cells were transferred to 96-well white plate at a cell density of $50x10^3$ cells per well and grown for an additional 24 h. The growth medium was removed and cells charged with 10 μM coelenterazine (Gold Biotechnology, St. Louis, MO) in the presence of 30 μM reduced glutathione (Sigma-Aldrich, St. Louis, MO) in ECB buffer (20 mM HEPES pH 7.4, 140 mM NaCl, 20 mM KCl, 5 mM Glucose, 1 mM $MgCl_2$, 1 mM $CaCl_2$) for 2 hours at 37°C and 95% air/5% CO_2. Charging buffer was replaced with ECB buffer (50 μl) and bioluminescence signals were detected for 30 s after 50 μl injection of 2x concentrated agonist in ECB using a Luminoskan Luminometer (Labsystems, Franklin, MA) or EnVision multilabel plate reader (Perkin Elmer). For desensitization assays and to test antagonist and inverse agonist effect on Ca^{2+} mobilization, cells were collected from 6 well plate 48 hours after transfection and charged for 2 hours in the dark by rotating at room temperature. Dose-dependence was measured by injecting 50 μl of cells ($50x10^3$) into wells of a 96-well plate containing 25 μl of 4x concentrated compound in ECB. Cells were incubated for indicated time periods and bioluminescence measurements were triggered by injection of 25 μl of 4x concentrated agonist in ECB; integrated luminescent signals were recorded for the first 30 s. Luminescence signals were normalized to total response after permeabilization with 0.1% Triton X-100.

Live cell Ca^{2+} mobilization assays in neuronal SH-SY5Y cells and primary hypothalamic neurons were performed with the Fluo-4 direct assay (Invitrogen). Briefly, SH-SY5Y and SH-GHSR1a cells were seeded on poly-D-lysine coat-well glass chambers and transfected with SNAP-DRD2. 48 hours after transfection cells were stained for SNAP-DRD2 expression by labeling with 2 μM of BG-647 dye (SNAP-Surface 647, New England Biolabs, Beverly, MA) in growth medium supplemented with 0.5% FBS for 30 min. After washing, cells were incubated with Fluo-4 in ECB for 45 min at 37°C and 95% air/5% CO_2. Cells were incubated for 15 min at room temperature before treatment. Buffer was exchanged to ECB, and after agonist injection $[Ca^{2+}]$ changes were measured with a laser scanning confocal Olympus FluoView 1000 system. The fluorescent emission images were collected every 1 sec for a period of 2 min and image data analyzed by the FluoView software (Olympus). The relative fluorescence intensity change ($\Delta F=F-F_o$) over background was calculated ($\Delta F/F_o$) and data presented as percentage of maximal response.

Live Cell Time Resolved (Tr)-FRET. Labeling of cells was performed after 48 hours of transfection as described previously (Maurel et al., 2008). Briefly, for the SNAP/CLIP assay with transfected constructs cells were incubated in the presence of 100 nM of donor, benzyl guanine conjugated terbium cryptate BG-TbK (SNAP-Lumi4-Tb, Cisbio), and 250 nM of acceptor, benzyl cytosine conjugated d2 fluorophore BC-647 (SNAP-surface 647, New England Biolabs), for 1 h at 37°C (95% air/5% CO_2) in DMEM and 0.5% FBS. Cells were washed twice with Tris-KREBS buffer (20 mM Tris pH7.4, 118 mM NaCl, 5.6 mM glucose, 1.2 mM KH_2PO_4, 1.2 mM $MgSO_4$, 4.7 mM KCl and 1.8mM $CaCl_2$) and Time-resolved (Tr) FRET signals measured at 665 nm and 620 nm after excitation at 337 nm with 50 μs delay and integration time 400 μs using an EnVision multilabel plate reader. The background signal was calculated from cells labeled with

donor BG-TbK (100 nM) without acceptor. The ratio of fluorescence (665 nm/620 nm) was calculated for each sample and the ΔF (fluorescence ratio for the sample - fluorescence ratio of a background) was calculated and results presented as a percentage of maximal fluorescence ratio. For Tr-FRET receptor titration assays, cell surface expression of HA-CLIP-receptor variants was determined by cell surface ELISA (Kern et al., 2007).

Tr-FRET binding assays. Fluorescently-labeled ghrelin (red-ghrelin from Cisbio) binding assays were performed on batch labeled cells with terbium-cryptate. 48 h after transfection with SNAP-tagged receptors, cells were labeled with 100 nM of BG-TbK (Cisbio) substrate in 6-well plates by incubating for 1 h at 37°C (95% air/5% CO_2) in DMEM containing 0.5% FBS. Cells were then detached, collected by centrifugation (1000 x g, 10 min) and washed three times with PBS. Pelleted cells were resuspended in Tris-KREBS buffer and seeded in 96-well plates ($50x10^3$ cells per well). Saturation binding assays were performed by incubating the cells with increasing concentration of red-ghrelin diluted in Tris-KREBS. Non-specific binding was determined by adding 100X unlabeled ghrelin at each red-ghrelin concentration. Plates were incubated for 2 h at 4°C in the dark and Tr-FRET signals measured using the EnVision plate reader as described above for Tr-FRET assays. For competition binding assays, both red-ghrelin and the unlabeled compound were diluted in Tris-KREBS buffer. Batch labeled cells with 100 nM BG-TbK were distributed to 96-well plates at density of 50 x 10^3 cells/well and incubated with 12.5 nM of red-ghrelin in the presence of increasing concentrations of competitor. Plates were than incubated for 2 h at 4°C and Tr-FRET signal detected as described above with the EnVision plate reader.

Tr-FRET assay on membrane preparations from mouse brain. Mouse brains were dissected as above, tissues lysed and homogenized on ice using a glass-Teflon tissue homogenizer in PMEP buffer (PBS, 50 mM mannitol, 2 mM EGTA, 0.5 mM phenylmethylsulfonyl fluoride, 1 mM dithiothreitol and protease inhibitor cocktails (Roche Diagnostics, Manheim, Germany). Undisrupted cells and tissue debris were removed by centrifugation (1000 x g, 10 min at 4°C), the supernatant centrifuged for 60 min at 32,000 x g, 4°C and the pellet containing membranes resuspended in PMEP buffer to obtain 1-2 mg/ml protein concentration. Membranes were aliquoted and stored at -80°C. Protein concentration was measured using the Bradford assay (Bio-Rad). To perform Tr-FRET, 200 μg membranes were labeled with biotin using 5 mM Sulfo-NHS-LC-Biotin (Pierce Biotechnology) and biotinylated membranes (20 μg/well) were suspended in TMEP (50 mM Tris pH 7.4, 50 mM mannitol, 2 mM EGTA, 0.5 mM phenylmethylsulfonyl fluoride) containing 1 mM dithiothreitol and protease inhibitor cocktails (Roche Diagnostics) and added to streptavidin coated 96-well plates (Greiner Bio-One Gmbh, Frickenhause, Germany) then incubated for 2 h at 4°C in the dark. Red-ghrelin (100 nM) and mouse anti-DRD2 antibody (1:100 dilutions, Santa Cruz Biotechnology) were added and the plates incubated overnight at 4°C in the dark. To measure the background signal membranes were incubated with 100 nM of red-fluorophore and mouse anti-DRD2 antibody. Plates were washed twice with TMEP and incubated with terbium-kryptate labeled anti-mouse antibody (10 nM/well; Cisbio) for 2 h at 4°C in the dark. After two final washes, 400 mM KF in TMEP was added to each well and Tr-FRET signal was measured using an EnVision plate reader as described above.

FRET microscopy on brain slices. Mouse brain sections (20 μm) were processed for FRET studies. Sections were incubated with 100 nM red-ghrelin (Cisbio) in a humidified chamber

overnight at 4°C in the dark. Sections were washed with cold PBS and fixed with 4% paraformaldehyde in PBS. After washing with PBS, slices were blocked in the presence of 1% BSA in PBS for 1 hour and incubated with mouse anti-drd2 antibody (1:100 dilutions, Santa Cruz Biotechnology) in 0.1% BSA/PBS solution at room temperature for 1 hour in the dark. After three washes with 0.1% BSA/PBS, sections were incubated with secondary goat anti-mouse Cy3 labeled antibody (Invitrogen, 1:100 dilution) at room temperature for 1 hour in the dark. Slides were then mounted with Vectashield and FRET microscopy performed using confocal Olympus FluoView 1000. Images were acquired with a 60x/NA:1.42 objective, with the donor excited by a laser at 543 nm and the acceptor excited by a laser at 635 nm; emissions were collected with 560 nm and 655 nm filters. Images were acquired for FRET analysis as described in an algorithm by Chen Y et al (Chen et al., 2005). The processed FRET images were generated based on this algorithm by using FluoView software. The rate of energy transfer efficiency and the distance between the donor and acceptor molecules were calculated by selecting small regions of interest (ROI) using FluoView software.

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Supplementary figure legends

Figure S1. Validation of mouse DRD2 antibody.

(a) Titration of mouse DRD2 antibody by cells surface ELISA in HEK293 cells (left panel). Cells were transfected with empty vector, HA-SNAP-DRD2, HA-SNAP-DRD1 or HA-SNAP-GHSR1a. After fixation cells were labeled with increasing concentration of mouse DRD2 antibody (1:1000, 1:500, 1:100 and 1:50 dilutions) and secondary mouse antibody conjugated to HRP (1:1000 dilution). In control experiments, to show the expression of DRD2, DRD1 and GHSR1a on cell surface, we performed cell surface ELISA using mouse HA antibody on the same cells (right panel). These results show that only the DRD2 transfected HEK293 cells were labeled by cell surface ELISA.

(b) Only the DRD2 transfected HEK293 cells were labeled by immunofluorescence. HEK293 cells were transfected with HA-SNAP-DRD2 (top panel under lower and higher magnification), HA-SNAP-DRD1 (middle panel) or empty vector (lower panel) and immunofluorescence was performed by using mouse DRD2 antibody (1:100 dilution). For a control experiments, to show the expression of DRD1 and DRD2 the same cells were labeled with BG-647 (2 μM) for SNAP-tag detection.

(c and d) To show the specificity of DRD2 antibody we performed immunoflourescence staining on striatal and hypothalamic mouse brain slices from *drd2+/+* and *drd2-/-* mice. **(c)** Striatal brain slices were stained with mouse DRD2 antibody (1:100 dilution) and DAPI from *drd2 +/+* (bottom panels; under low and high magnifications) or *drd2 -/-* mice (lower panels; under low

and high magnifications). **(d)** Hypothalamic brain slices were stained with mouse DRD2 antibody (1:100 dilution) and DAPI from *drd2 +/+* (bottom panels; under low and high magnifications) or *drd2 -/-* mice (lower panels; under low and high magnifications).

Figure S2. In cells co-expressing GHSR1a and DRD2, dopamine-induced Ca^{2+} release is independent on constitutive activity of GHSR1a and not a result of signal integration.

(a) Effect of $G\alpha_q$ siRNA on constitutive activity of GHSR1a detected by IP_1 accumulation. Cells were transiently transfected with empty vector and control siRNA, GHSR1a and control siRNA or GHSR1a and $G\alpha_q$ siRNA. Overexpression of GHSR1a (GHSR1a + control siRNA) resulted significant ($P<0.01$) increase in IP_1 accumulation compared to cells expressing empty vector and control siRNA; however in cells co-expressing $G\alpha_q$ siRNA and GHSR1a the IP_1 production was significantly ($P<0.05$) reduced compared to the cells co-expressing GHSR1a and control siRNA. IP_1 accumulation was determined by using IP-One HTRF assay kit (Cisbio).

(b) Dopamine-induced Ca^{2+} mobilization after overexpression of $G\alpha_q$ subunit in cells coexpressing GHSR1a and DRD2.

(c) Dopamine-induced Ca^{2+} mobilization in cells co-expressing GHSR1a and DRD2 after pretreatment with BisI (1 μM, PKC inhibitor) for 1 h compared to untreated cells.

(d) Dopamine-induced (1μM) Ca^{2+} mobilization in cells co-expressing GHSR1a and DRD2 after preincubation with ghrelin (10 nM, ■) for 3 min or in the absence of ghrelin (●).

(e) Ghrelin-induced (10 nM) Ca^{2+} mobilization in cells co-expressing GHSR1a and DRD2 after preincubation with dopamine (1μM, ■) for 3 min or in the absence of dopamine (●).

(f) Mobilization of $[Ca^{2+}]_i$ in cells co-expressing GHSR1a and empty vector or GHSR1a and DRD2 after ghrelin treatment alone (10 nM), dopamine treatment alone (1μM) or simultaneous addition of ghrelin (10 nM) and dopamine (1μM). Simultaneous addition of ghrelin and dopamine together resulted in additive Ca^{2+} accumulation in cells co-expressing GHSR1a and DRD2.

The data represent the mean ± s.e.m. for each concentration point. n.s. not significant; * $P<0.05$ and ** $P<0.01$; versus control treatments.

Figure S3. Expression analysis, functional characterization and detection of homomers of the SNAP-GHSR1a in HEK293 cells.

(a) Receptor expression analysis by indirect ELISA using an HA antibody in cells transfected with empty plasmid, HA-GHSR1a or HA-SNAP-GHSR1a. Cell surface (black columns) and total (white columns) expression are shown as a percentage of the maximal expression. Total receptor expression was measured after permeabilization of cells with 0.25% Triton X-100.

(b) Ghrelin caused a dose-dependent increase in IP_1 accumulation in cells transfected with HA-GHSR1a or SNAP-GHSR1a. IP_1 accumulation was determined by using IP-One HTRF assay kit (Cisbio).

(c) Expression analysis of SNAP-GHSR1a by in-gel fluorescence SDS-PAGE. Membrane preparations (5 μg) from HEK293 cells transfected with empty vector or SNAP-GHSR1a were labeled in the presence of green fluorophore (20 μM of BG-488) and separated on 10 % SDS-PAGE, and fluorescence was detected at 488nm

(d) Cell surface expression of SNAP-GHSR1a detected by confocal microscopy. Cells transfected with empty vector or SNAP-GHSR1a were labeled in the presence of 2 μM of BG-488.

(e) Cells transfected with SNAP-GHSR1a or SNAP-tagged nuclear localized histone H2B (SNAP-H2B) were labeled with increasing concentration of non-cell permeable green fluorophore (BG-488) and fluorescent signal was detected using Gemini Fluorescence plate reader (Molecular Devices). Data are shown as a percentage of the maximal fluorescence signal.

(f and g) Detection of homomer formation between GHSR1a *in vitro* by Tr-FRET. **(f)** FRET signal is detected in cells expressing SNAP-GHSR1a with varying concentrations of BG-647 and 100 nM of BG-TbK. **(g)** FRET signal at the cell surface as a function of increasing amount of SNAP-GHSR1a transfected.

Figure S4. Characterization of homomerization of SNAP-DRD2 by Tr-FRET.

(a) To establish the optimal labeling conditions for SNAP-DRD2, FRET signal was detected in cells expressing SNAP-DRD2 with varying concentrations of BG-647 (acceptor fluorophore) and 100 nM of BG-TbK (donor fluorophore). In this case, we defined conditions for the equivalent labeling of SNAP-DRD2 with either fluorophore for detecting DRD2 homomers.

(b) Tr-FRET measurements from cells transfected with DRD2 after labeling with 100 nM of BG-TbK (donor) and 250 nM of BG-647 (acceptor). FRET signal is represented as a function of the increasing amount of transfected SNAP-DRD2 at the cell surface. Cell surface expression of HA-SNAP-DRD2 was determined by cell surface ELISA.

Figure S5. Cell surface expression of wild-type GHSR1a, M213K-GHSR1a and F279L-GHSR1a.

(a) Cell surface expression of WT-GHSR1a, M213K-GHSR1a and F279L-GHSR1a in transfected HEK293 cells determined by cell surface ELISA. The data represent the mean ± s.e.m. for each construct.

Figure S6. Detection GHSR1a:DRD2 heteromers *in vivo* by Tr-FRET: validation of red-ghrelin binding in HEK293 cells and in mouse brain slices.

(a) Total and non-specific FRET signal measured using red-ghrelin in cells expressing SNAP-GHSR1a after labeling with 100 nM of BG-TbK (left panel) and specific red-ghrelin binding detected in cells expressing SNAP-GHSR1a (right panel).

(b) Dose dependent competitive inhibition of red-ghrelin binding by unlabeled ghrelin and MK-677 but not by des-acyl ghrelin in cells expressing SNAP-GHSR1a after labeling with 100 nM of BG-TbK donor.

(c) Characterization of fluorescence ghrelin binding in mouse brain slices. Labeling of hypothalamic neurons using red-ghrelin in *ghsr* +/+ and *ghsr* -/- mice. Brain slices were stained in the presence of 200 nM red-ghrelin and cell nuclei stained with DAPI. Confocal microscopy was performed in hypothalamic neurons of *ghsr* +/+ (upper panel) and *ghsr* -/- (lower panel) mice. Specific red fluorescence signals were detected in neurons of *ghsr* +/+ mice.

(d) Dose dependent increase of FRET signals in cells co-expressing SNAP-GHSR1a and GHSR1a or SNAP-DRD2 and GHSR1a in the presence of increasing concentration of red-ghrelin and 100 nM of BG-TbK.

(e) Detection of heteromer formation between GHSR1a and SNAP-DRD2 *in vitro* by Tr-FRET using red-ghrelin. Tr-FRET assay were performed to determine heteromer formation between GHSR1a and DRD2 in HEK293. Dose dependent increase of FRET intensity signals in cells co-expressing different rations of GHSR1a to SNAP-DRD2 in the presence of increasing concentration of red-ghrelin and 100 nM of BG-TbK.

Data are shown as a percentage of the maximal FRET signal. The data represent the mean ± s.e.m. for each concentration point.

Figure S7. Cabergoline dose-dependently released Ca^{2+} in aequorin-HEK293 cells co-expressing GHSR1a with DRD2 and it dose-dependently reduced food intake in wild-type mice.

(a) Dose dependent effect of cabergoline on $[Ca^{2+}]_i$ mobilization in cells co-expressing GHSR1a and DRD2 (■), GHSR1a and empty vector (▲) or DRD2 and empty vector (▼). Cabergoline dose-dependently increased Ca^{2+} levels in cells co-expressing GHSR1 and DRD2.

(b) Effect of cabergoline administration on food intake in *ghsr* +/+ mice (n=8 for cabergoline and n=8 for vehicle). Mice were injected i.p. with cabergoline (0.5 mg/kg or 2 mg/kg) in 100 μl of physiological saline or with 100 μl saline alone (vehicle). Food intake was measured at 1, 2, 4,

20 h after injections. ***, P<0.001 cabergoline treated versus control vehicle treatments; ##, P<0.01 and ###, P<0.001 cabergoline treatments 2 mg/kg versus 0.5 mg/kg.

Figure S1. (Kern et al)

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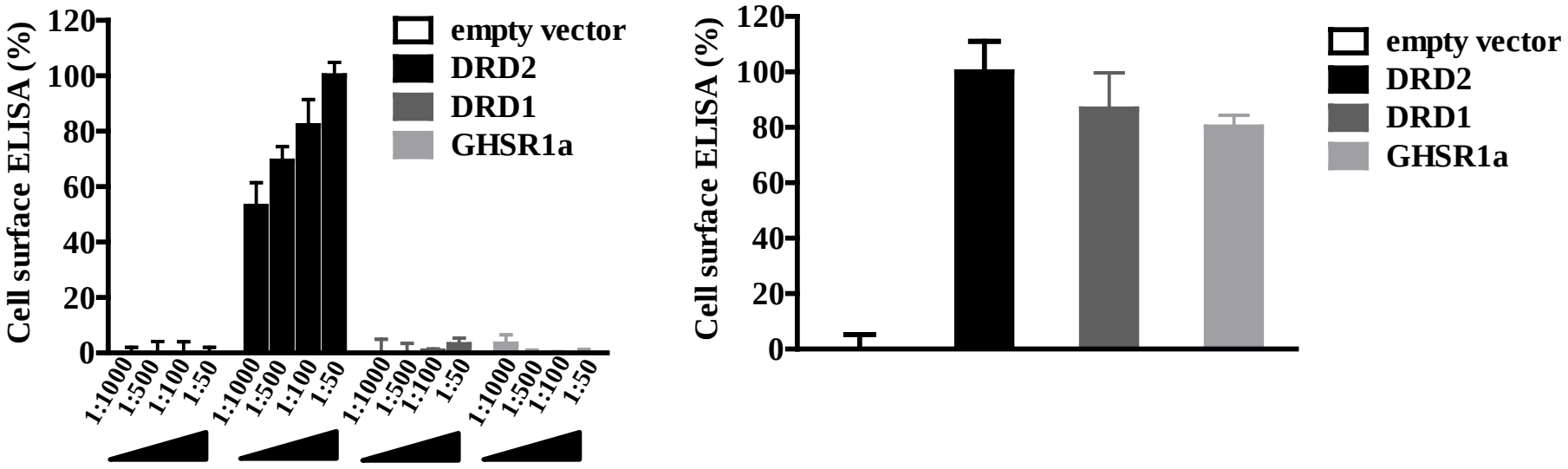

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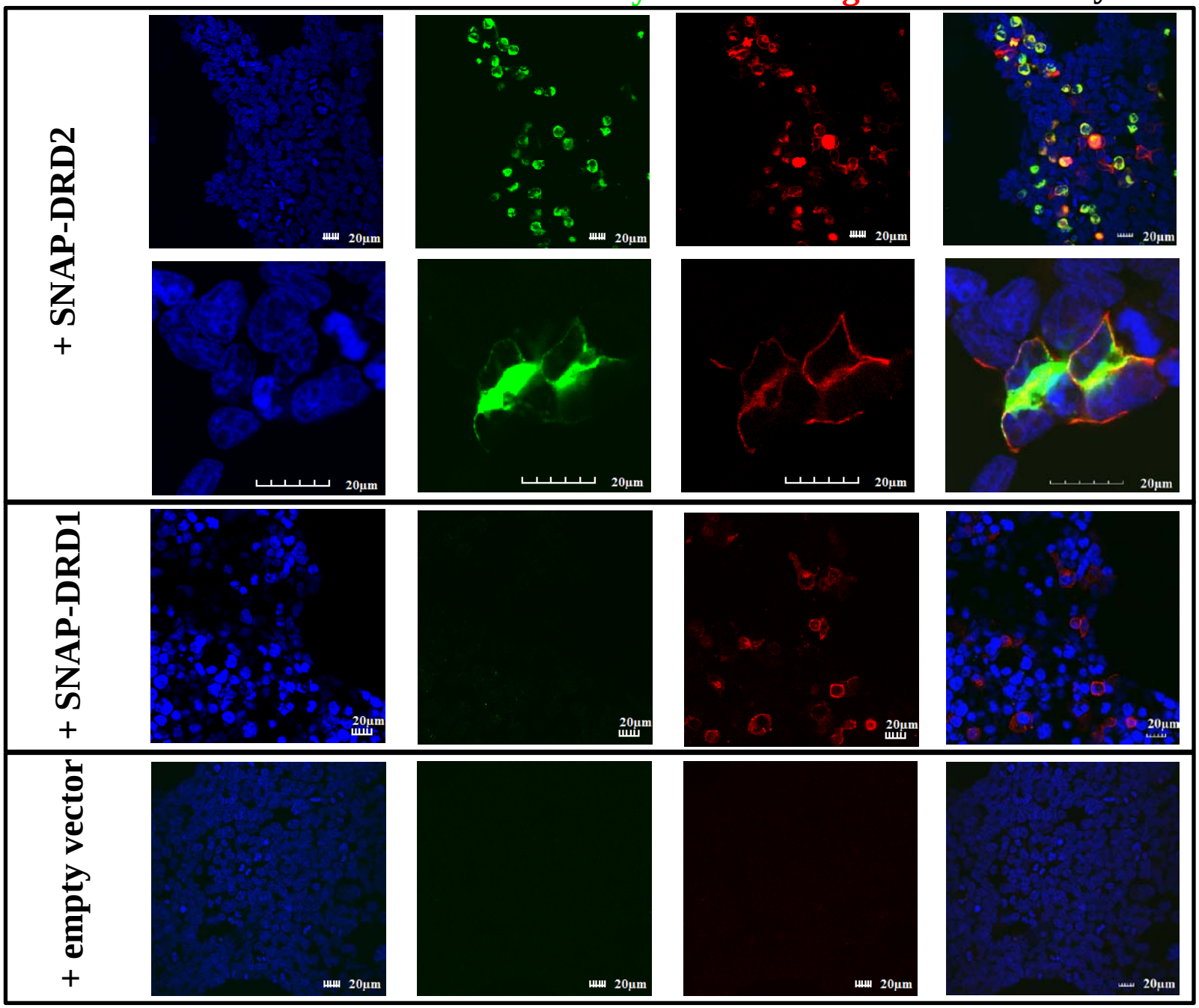

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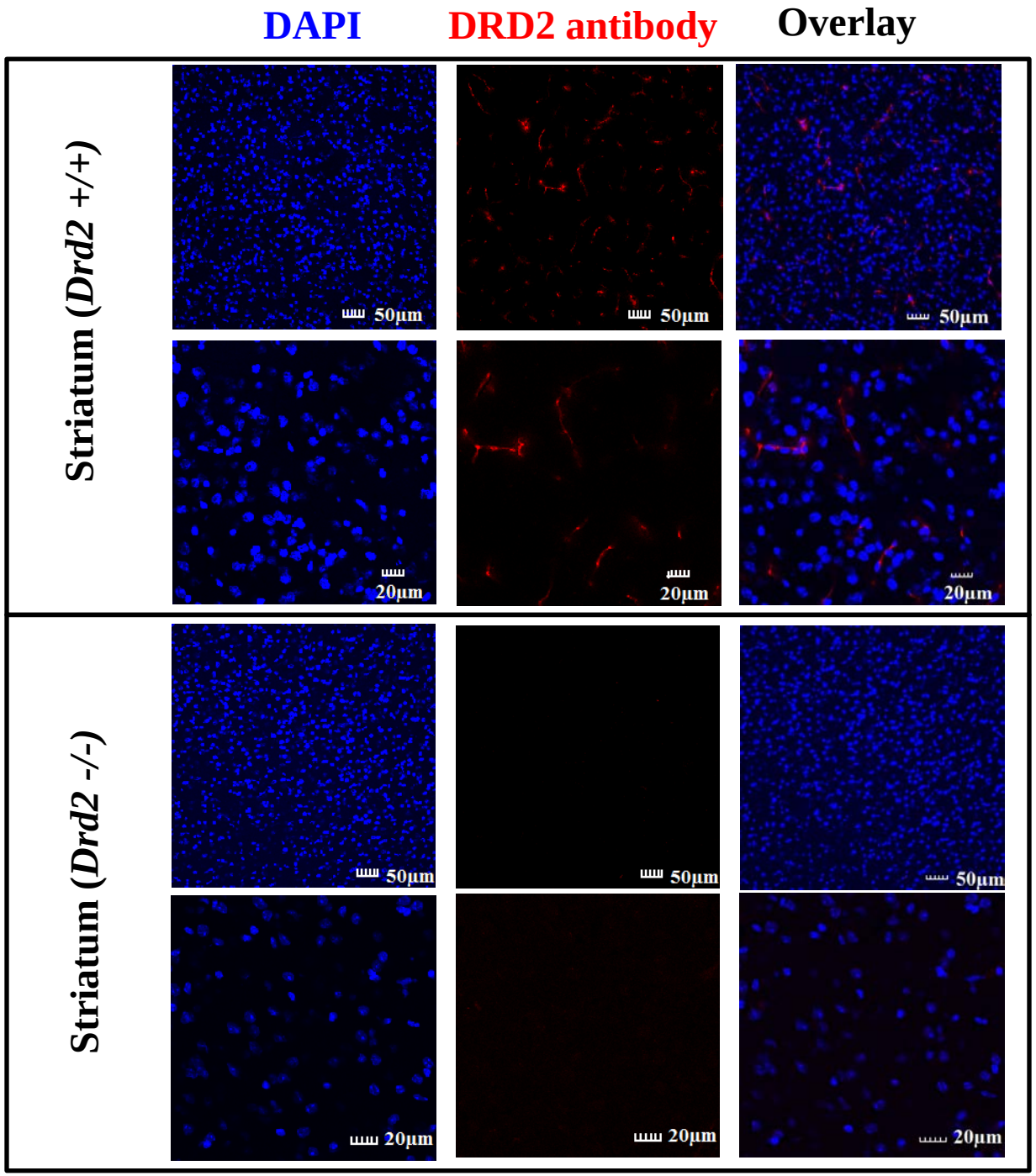

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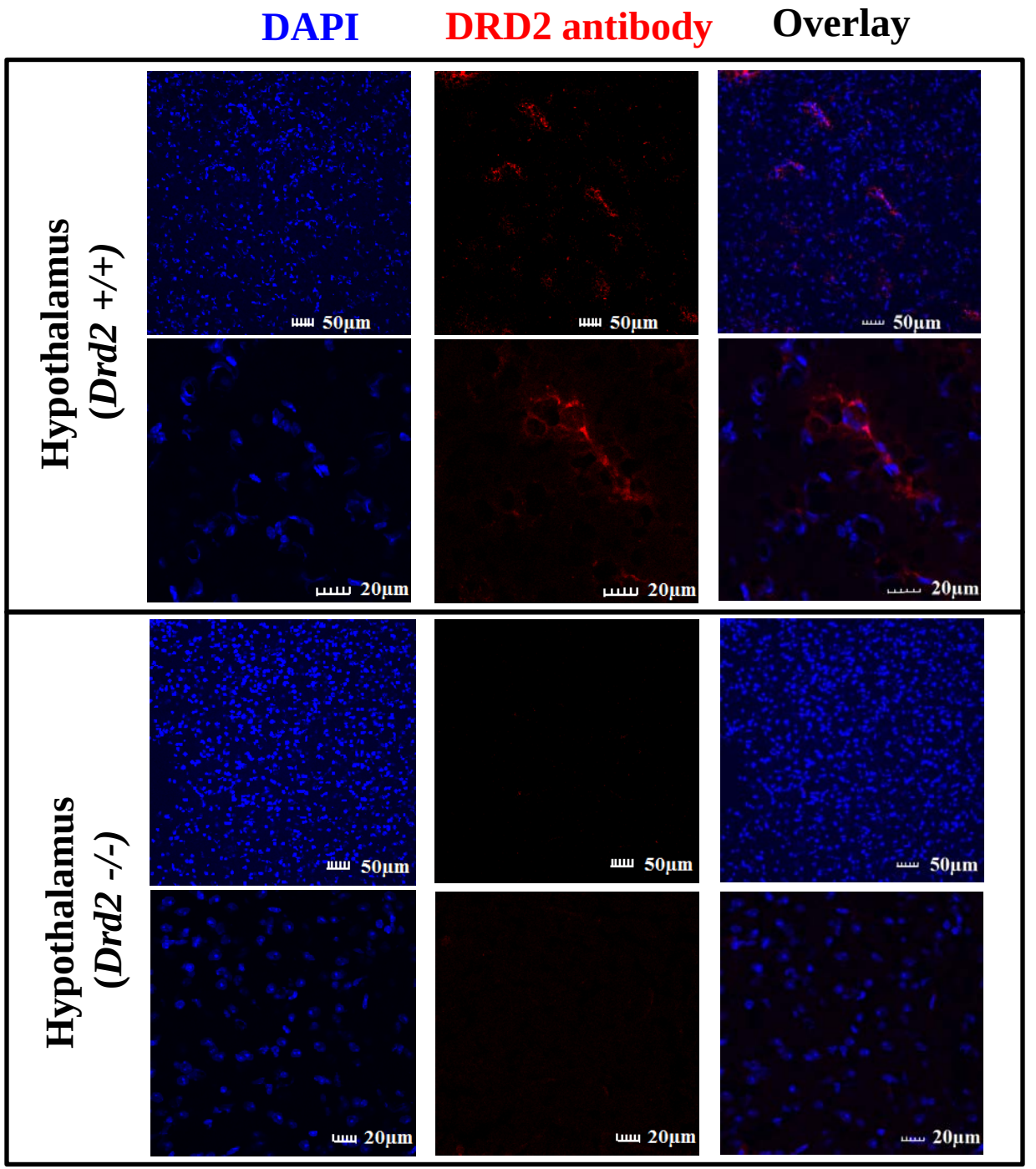

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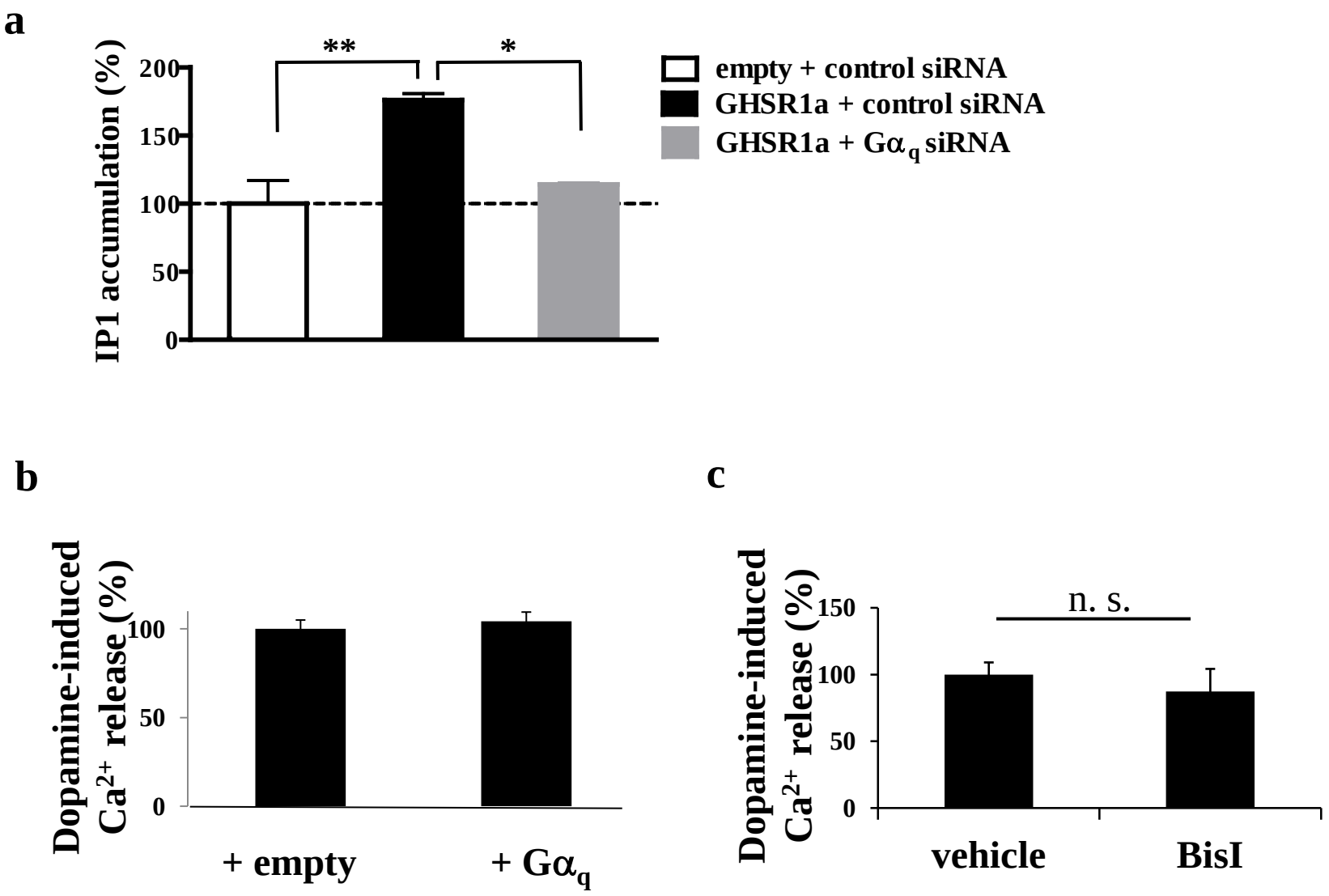

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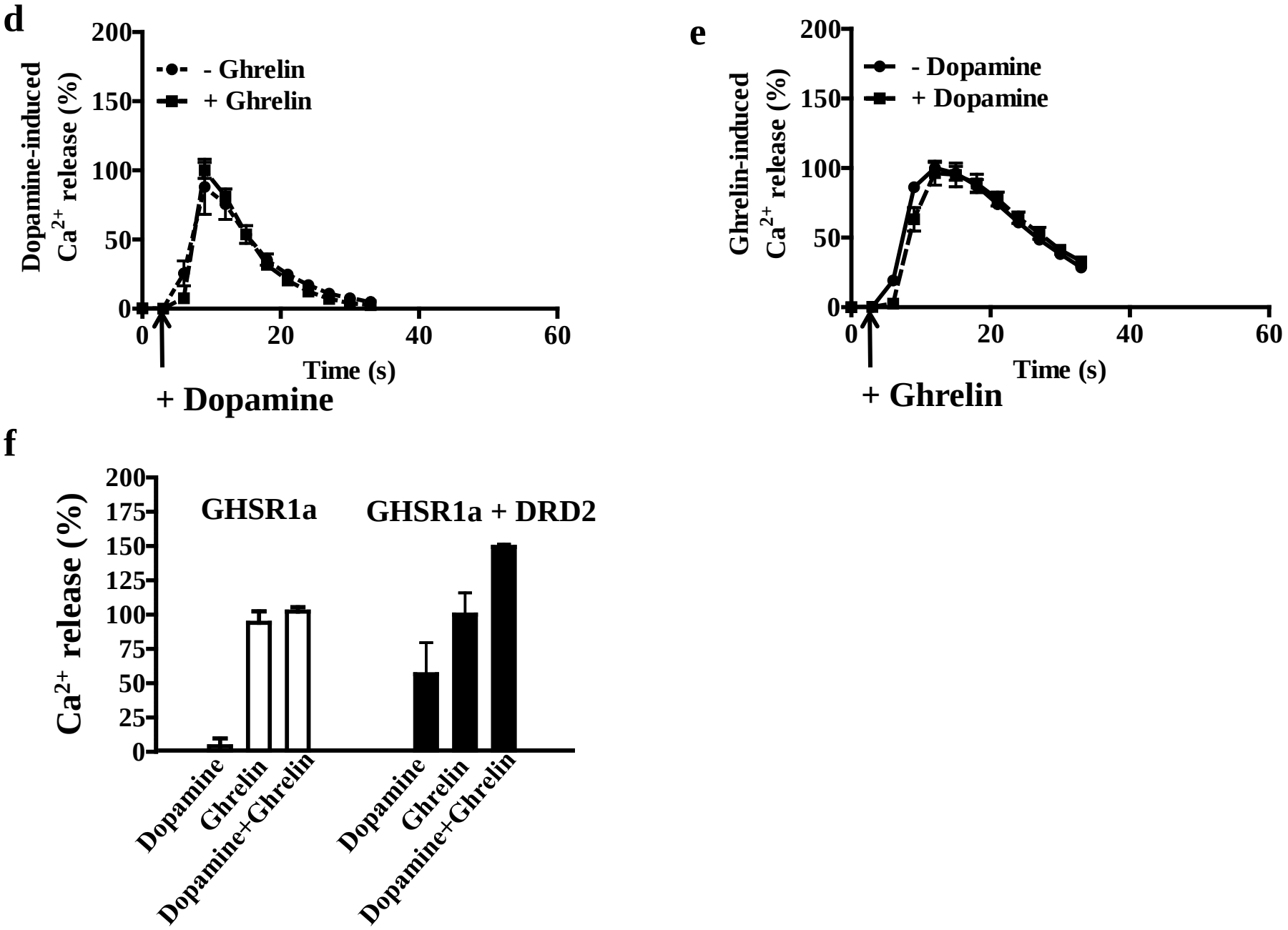

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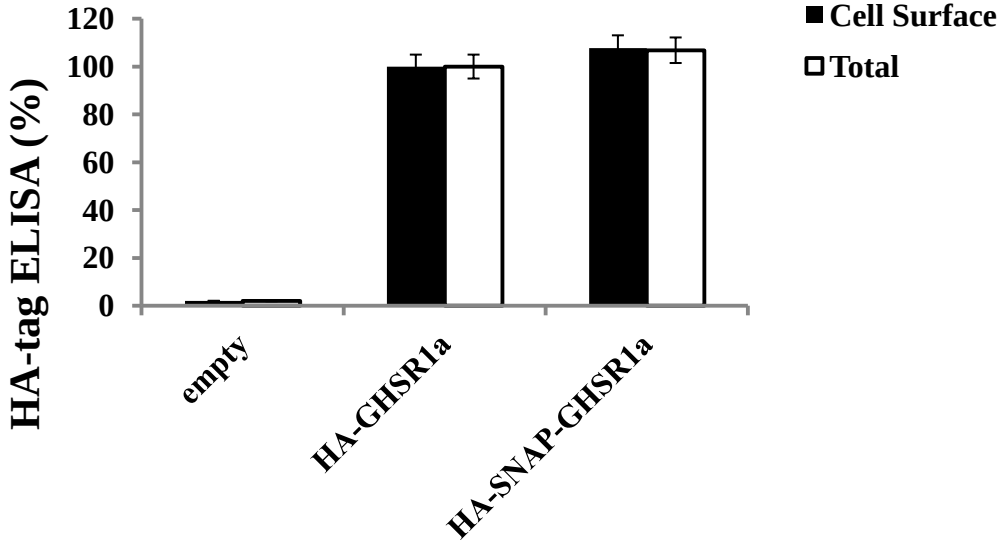

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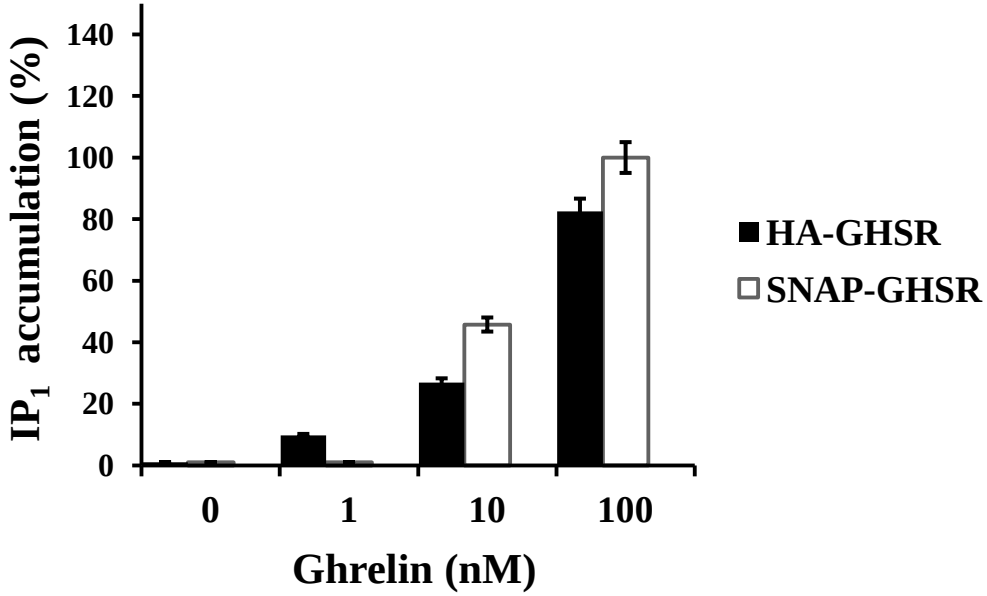

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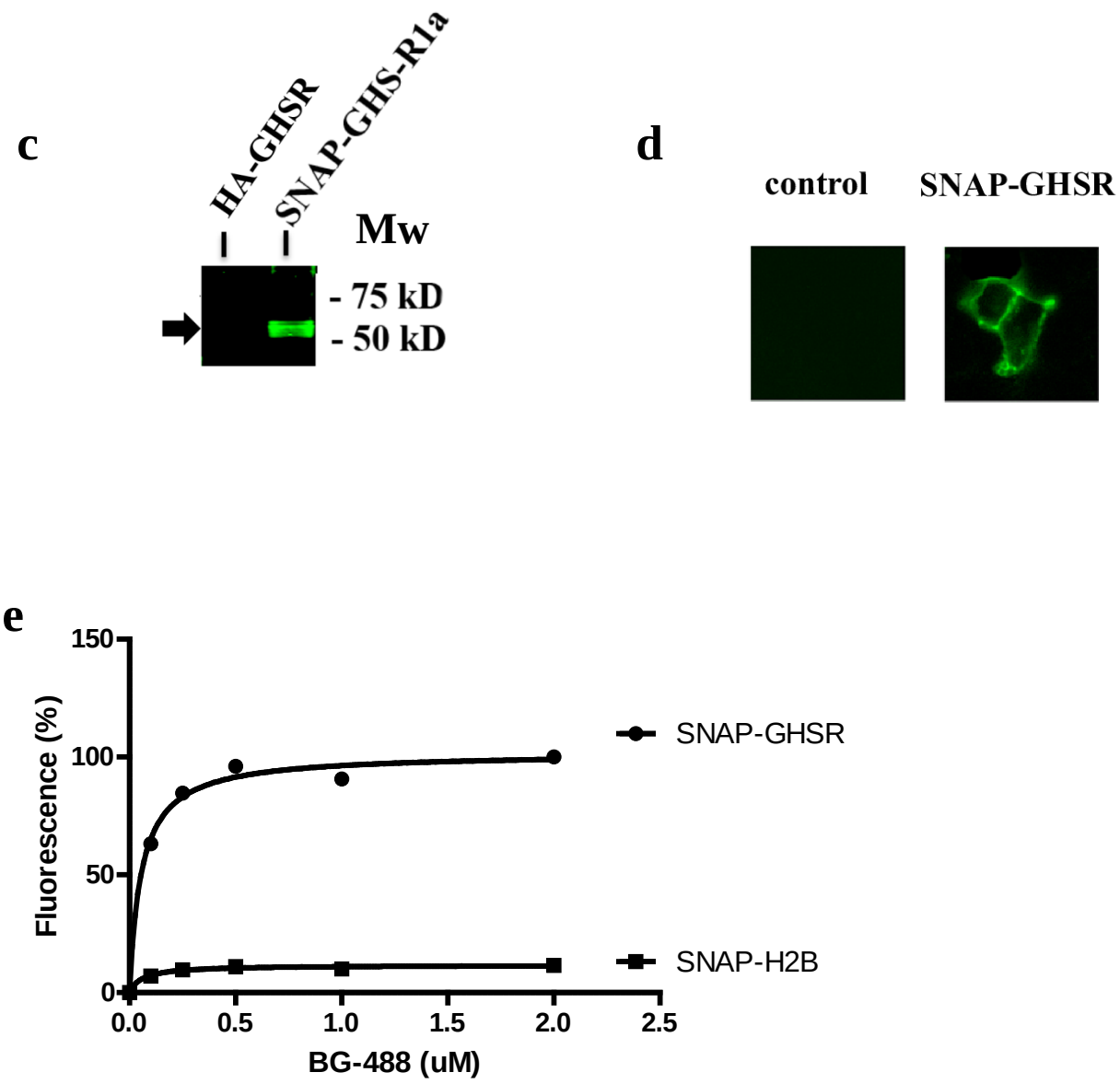

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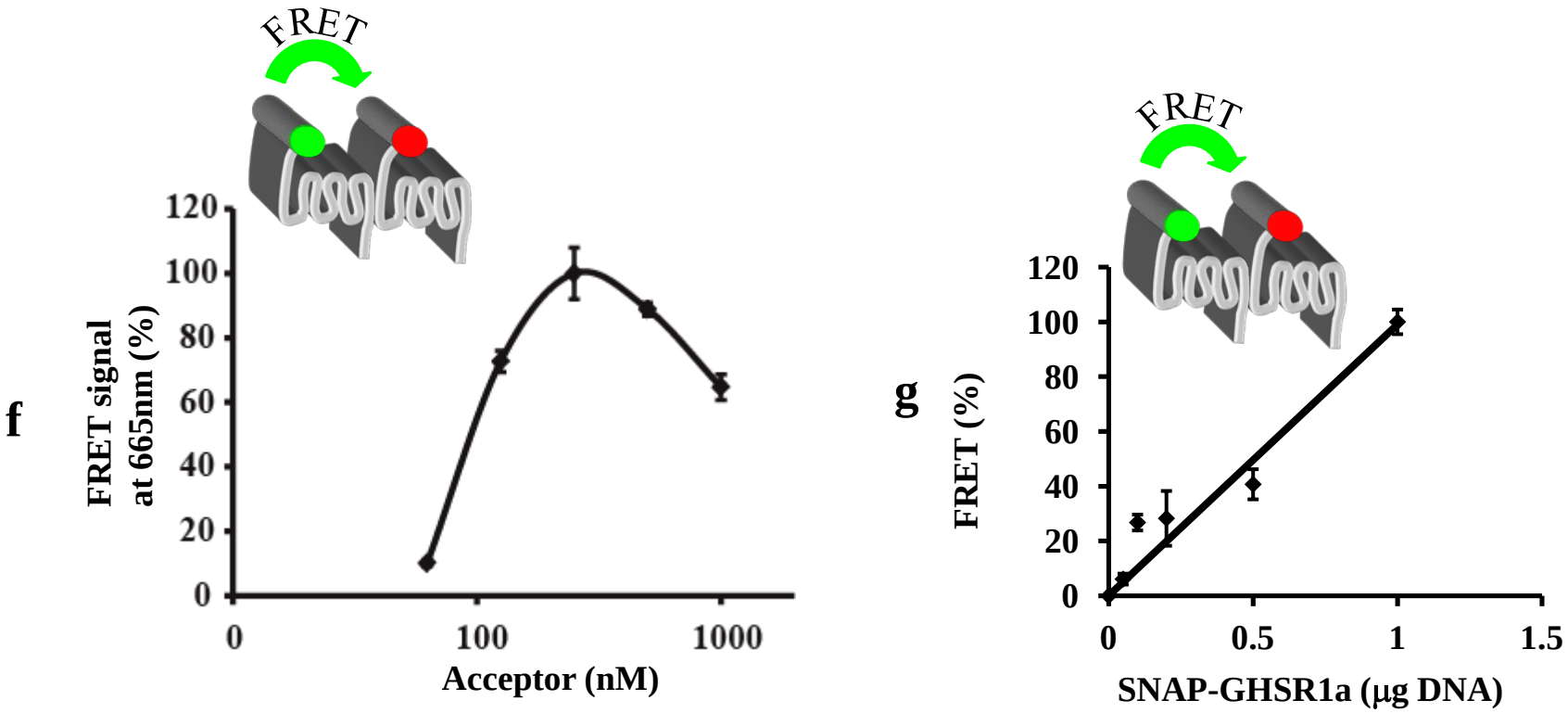

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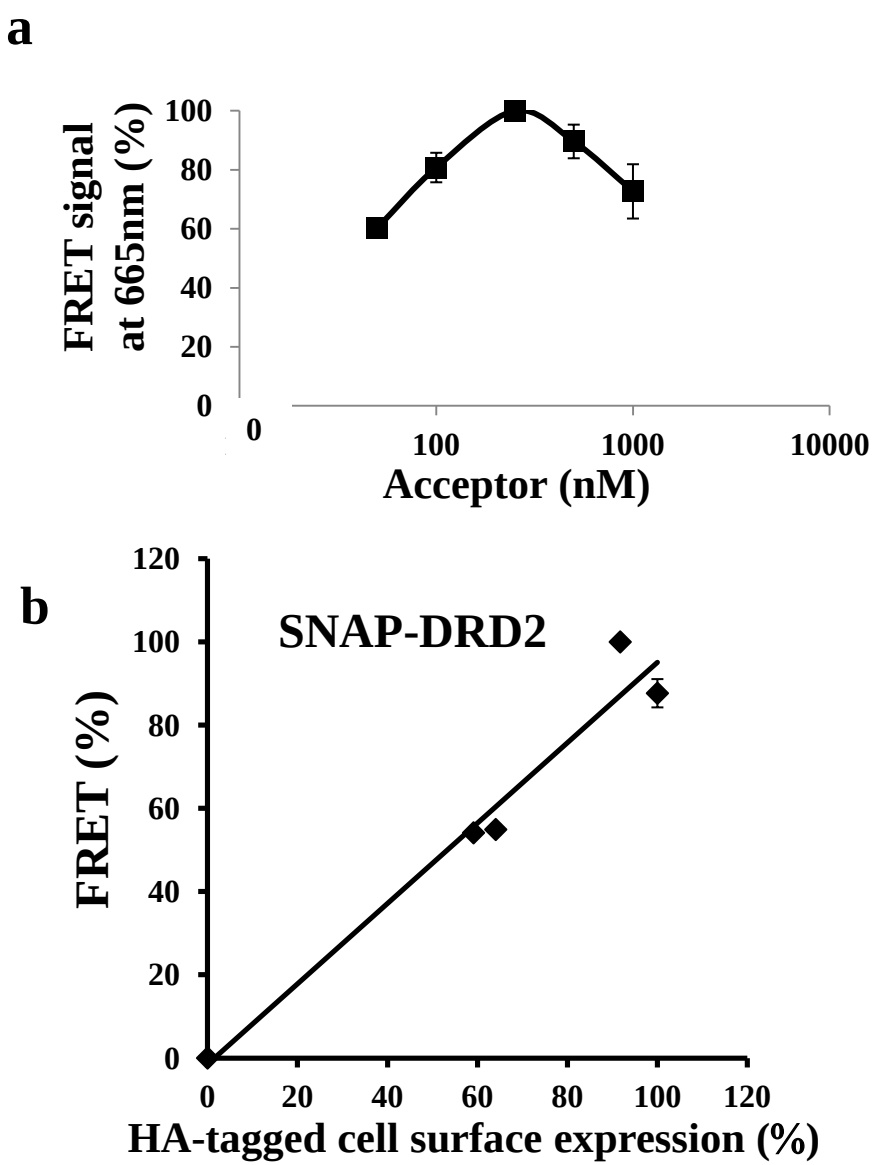

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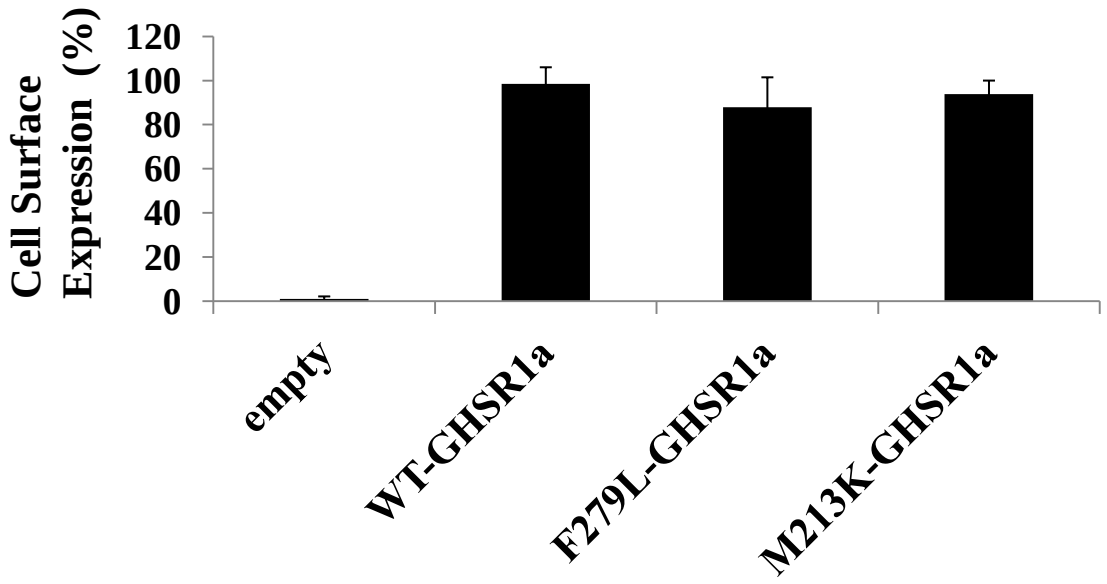

Figure S6. (Kern et al)

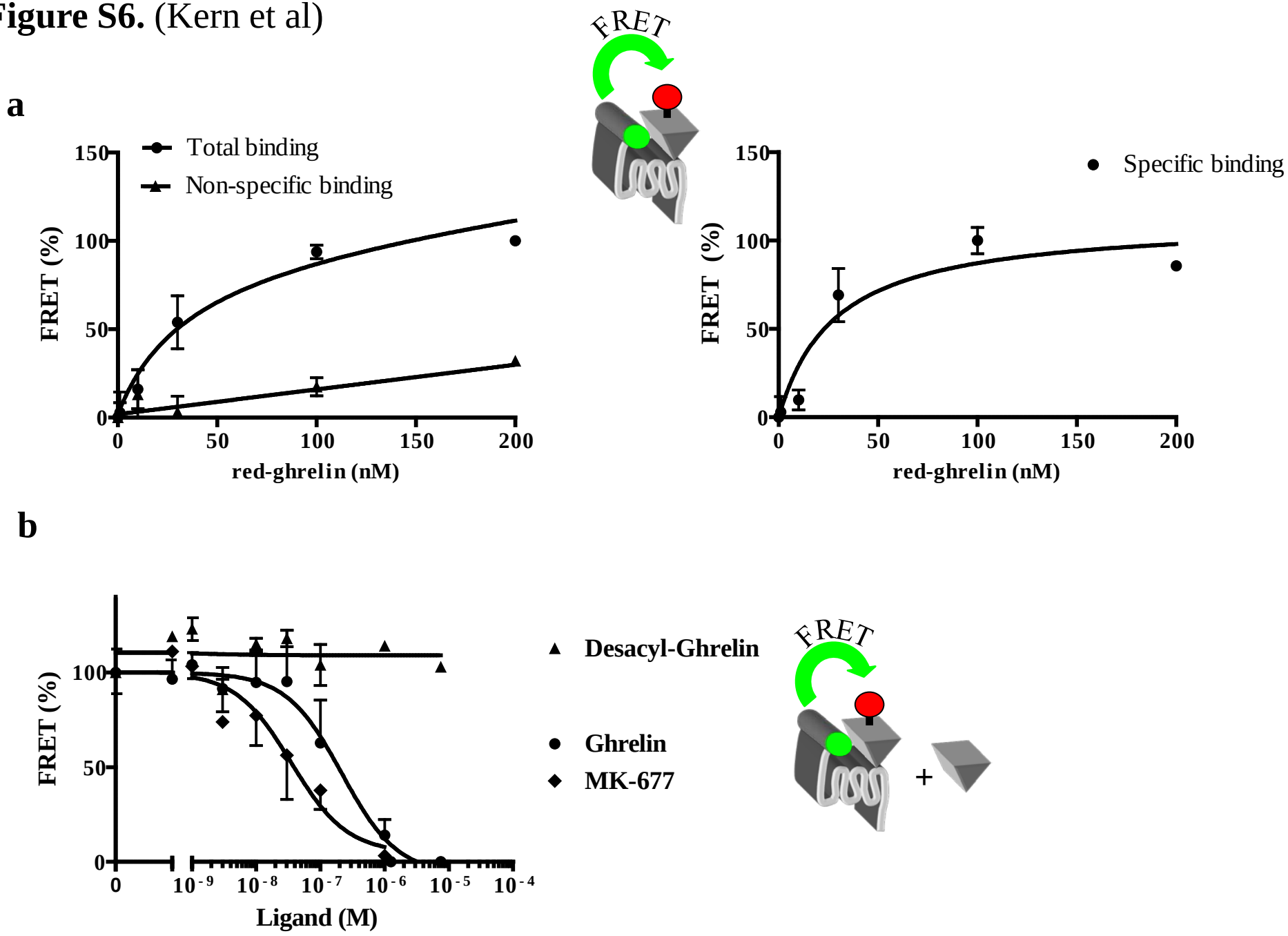

Figure S6. (Kern et al)

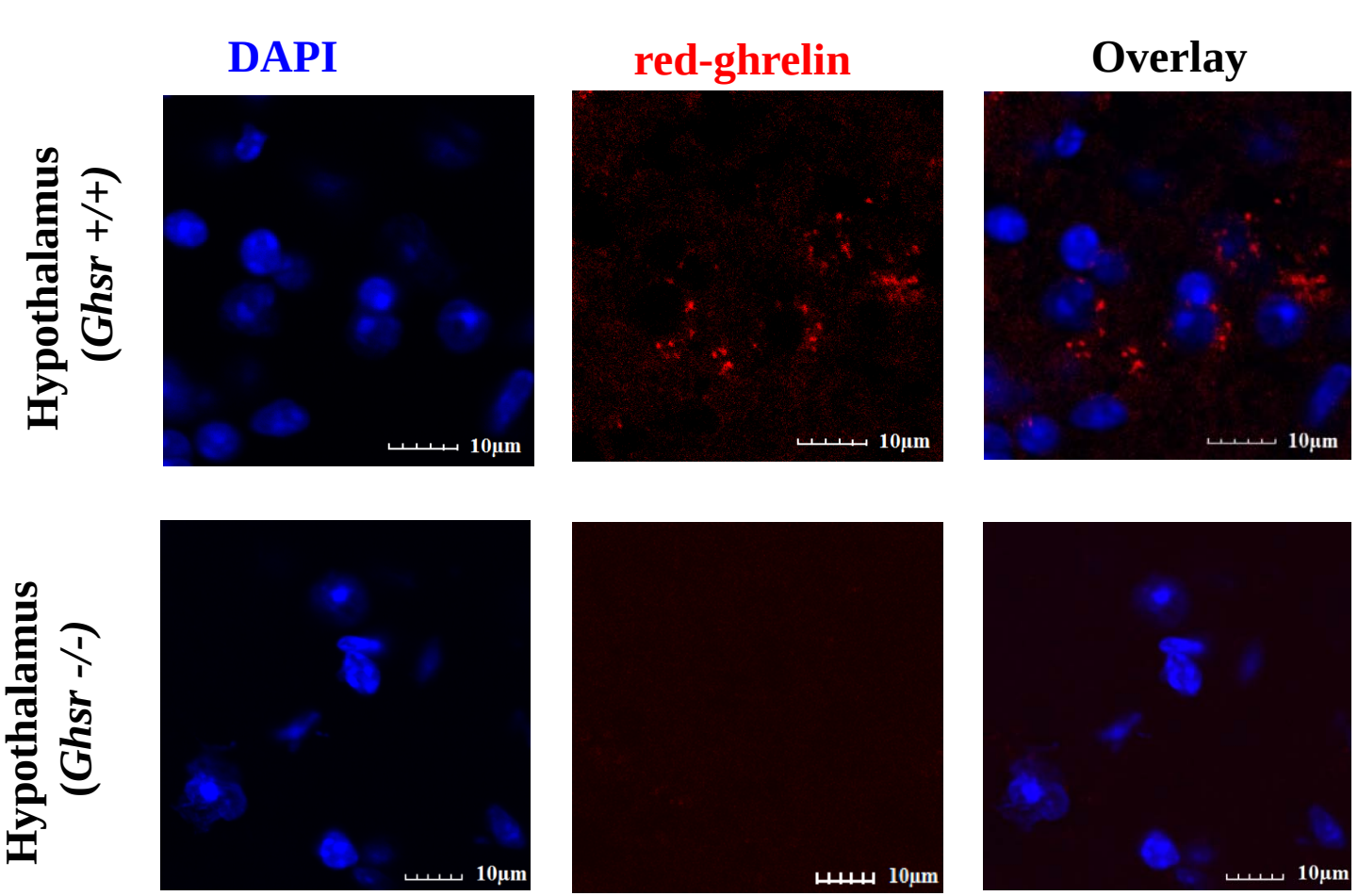

Figure S6. (Kern et al)

d

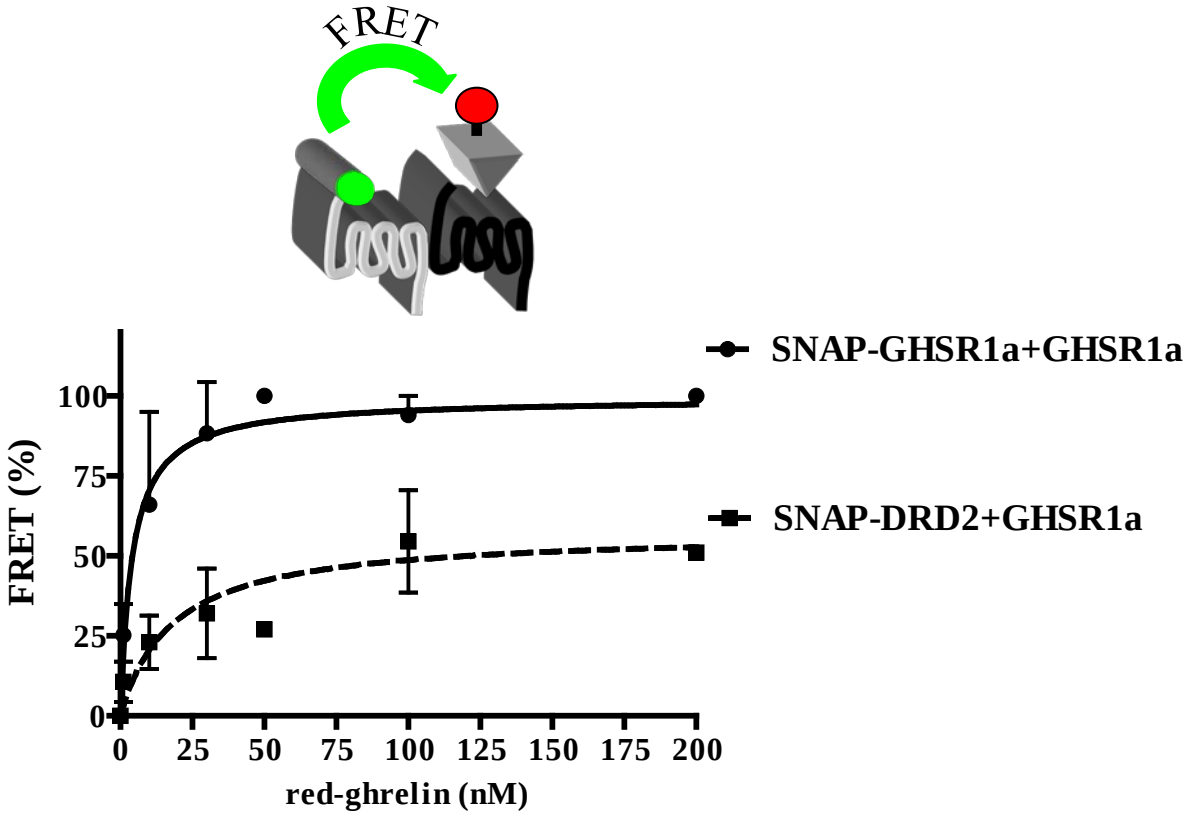

Figure S6. (Kern et al)

e

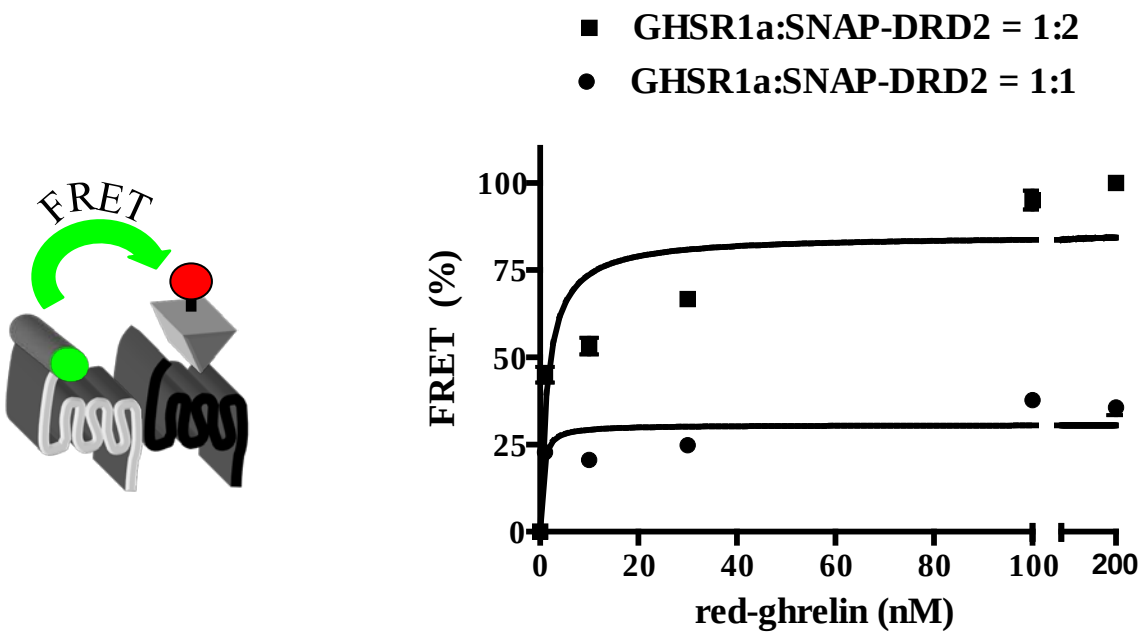

Figure S7. (Kern et al)