eurofins | Discovery Services

PRODUCT DATASHEET

Ready-to-Assay™ FSH Glycoprotein Hormone Receptor Frozen Cells

CATALOG NUMBER: HTS178LRTA

CONTENTS: Pack contains 2 vials of mycoplasma-free cells, 1 ml per vial. Fifty (50) mL of Media Component.

STORAGE: Vials are to be stored in liquid N_2. Media Component at 4ºC (-20ºC for prolonged storage).

BACKGROUND

Ready-to-Assay™ GPCR frozen cells are designed for simple, rapid calcium assays with no requirement for intensive cell culturing. Eurofins Discovery Services has optimized the freezing conditions to provide cells with high viability and functionality post-thaw. The user simply thaws the cells and resuspends them in media, dispenses cell suspension into assay plates and, following overnight recovery, assays for calcium response.

ChemiBrite cells co-express a GPCR along with a novel variant of clytin, a calcium-activated photoprotein, to enable sensitive luminescent detection of ligand-induced calcium flux. The ChemiBrite version of clytin contains a mutation that increases its affinity for calcium to a level that permits detection of cytosolic calcium in many cells with greater sensitivity than other mitochondrially expressed photoproteins. Luminescent calcium assays offer several advantages over fluorescent calcium assays including; lower substrate cost, increased sensitivity, and lack of interference from fluorescent compounds.

Follicular Stimulating Hormone (FSH) is a critical hormone in mammalian reproduction. In concert with Luteinizing Hormone (LH), this gonadotropin is secreted by the pituitary gland as a glycoprotein and affects all aspects of fertility and reproduction. In females, FSH drives ovarian development, maturation and cycle regulation. In males, FSH mediates spermatid maturation. FSH receptors couple to $G_{\alpha s}$ thus utilizing cAMP production to mediate cellular effects (Verrier et al). Cloned human FSH receptor-expressing ChemiBrite cells were made by stable transfection of HEK293 cells with ChemiBrite clytin, the FSH receptor (FSHR) and a promiscuous G protein to couple the receptor to the calcium signaling pathway, then cryopreserving the cells at an optimal time post-transfection. Upon thaw, recovery, and loading, the cells are ready for luminescent, fluorescent, and cAMP analysis of agonists, antagonists and modulators at the FSH receptor.

USE RESTRICTIONS

Please see User Agreement (Label License) for further details. ***One such restriction is that the contents of the supplied vial(s) are limited to a single use and shall not be propagated and/or re-frozen by licensee.***

WARNINGS

For Research Use Only; Not for Use in Diagnostic Procedures
Not for Animal or Human Consumption

GMO

This product contains genetically modified organisms.
Este producto contiene organismos genéticamente modificados.
Questo prodotto contiene degli organismi geneticamente modificati.
Dieses Produkt enthält genetisch modifizierte Organismen.
Ce produit contient organismes génétiquement des modifiés.
Dit product bevat genetisch gewijzigde organismen.
Tämä tuote sisältää geneettisesti muutettuja organismeja.
Denna produkt innehåller genetiskt ändrade organismer.

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APPLICATIONS

Calcium Flux Assays: Luminescent Mode and Fluorescent Mode; cAMP accumulation

APPLICATION DATA

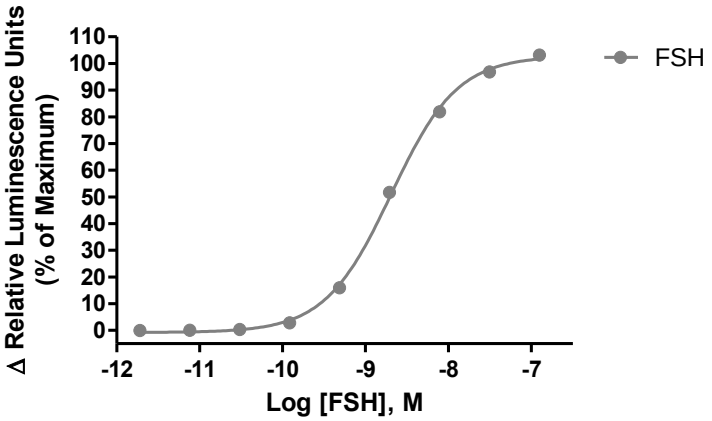

Figure 1. Representative data for activation of FSH receptor stably expressed in HEK293 cells induced by FSH using a luminescent calcium flux assay. FSH–expressing HEK293 cells were loaded with 10 µM coelenterazine for 2h at room temperature and calcium flux in response to the indicated ligand was determined on a Molecular Devices FLIPR^{TETRA}® with ICCD camera in 96-well format with a final concentration of 0.5% DMSO. Luminescence signal obtained in this experiment was 61,000 RLU (Relative Light Units) as measured by AUC (are under curve) for 80s post agonist addition using the provided protocol.

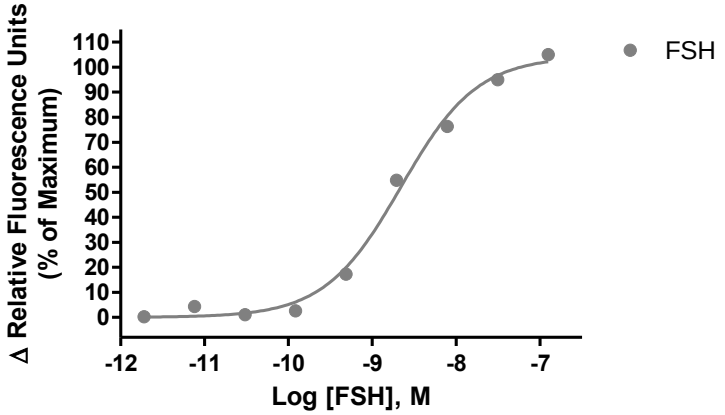

Figure 2. Representative data for activation of FSH receptor stably expressed in HEK293 cells induced by FSH using a fluorescent calcium flux assay. FSH–expressing HEK293 cells were seeded into a 96-well plate and the following day the cells were loaded with a calcium dye. Calcium flux in response to the indicated ligand with a final concentration of 0.5% DMSO was determined on a Molecular Devices FLIPR^{TETRA}® with ICCD camera. Maximal fluorescence signal obtained in this experiment was 26,000 RLU.

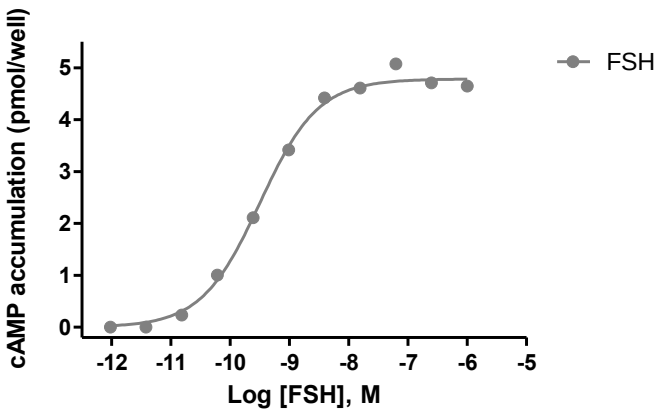

Figure 3. Representative data for activation of FSH receptor stably expressed in HEK293 cells induced by FSH using a cAMP accumulation assay. FSH–expressing HEK293 cells were seeded into a 96-well plate, and the following day the cells were treated with FSH for 15 minutes in the presence of 100 µM IBMX to determine receptor-mediated cAMP generation using a time-resolved fluorescence resonance energy transfer (TR-FRET) assay measured on the BioTek Synergy.

Table 1. Comparison of EC_{50} values of FSH-expressing HEK293 cells.

LIGAND	ASSAY	POTENCY (nM)	REFERENCE
FSH	Calcium Flux - Luminescence	2	Eurofins Internal Data
FSH	Calcium Flux - Luminescence	2.2	Eurofins Internal Data
FSH	cAMP accumulation	0.3	Eurofins Internal Data

ASSAY SETUP—Luminescence

1. Immediately upon receipt, thaw cells or place cells in liquid nitrogen.
2. Thaw included plating media at 4 ºC, warm to 37ºC prior to thawing cells.
3. Thaw cells rapidly by removing from liquid nitrogen and immediately immersing in a 37ºC water bath. Immediately after ice has thawed, sterilize the exterior of the vial with 70% ethanol.
4. Add 1mL of pre-warmed culture media to vial. Place contents from the vial into a 15 mL conical tube and bring the volume to 9 mL with culture media.
5. Centrifuge the cell suspension at 190 x g for six minutes
6. Remove supernatant and add 10.5 mL of pre-warmed culture media to resuspend the cell pellet.
7. Seed cell suspension into black Poly-D-Lysine (clear bottom) plate (100 µL/well for 96-well plate, 25 µL/well for 384-well plate).
8. When seeding is complete, place the assay plate at room temperature for 30 minutes.
9. Move assay plate to a humidified 37ºC 5% CO_2 incubator for 18-24 hours.
10. Next day prepare Assay buffer (HBSS, 20mM HEPES, pH 7.4) and Loading buffer (Assay buffer with 10 µM coelenterazine). *Note: Please prepare coelenterazine stock according to Mfg Recommendations at 10mM to allow for 1:1000 dilution into Loading buffer (10uM final). It is critical that coelenterazine solution is prepared at room temperature and is protected from light.*

11. Remove media from assay plate by inverting and tapping/flicking plate.
12. Add Loading buffer to assay plate (100 µL/well for 96-well plate, 25 µL/well for 384-well plate) and incubate plate for 4 hrs at room temperature, protected from light.
13. Prepare Ligand plate at 3x final concentration in Assay Buffer for 96-well assay plates (2x final concentration for 384-well plate)
14. Create Protocol for ligand addition. Please refer to FLIPR^{TETRA}® settings provided in Table 2. Set time course for 180 seconds, with ligand addition at 10 seconds.
15. After the run is complete, apply subtract bias on sample 1 and export data to analyze using the area under the curve statistic.

ASSAY SETUP—Fluoresccence

1. Immediately upon receipt, thaw cells or place cells in liquid nitrogen.
2. Thaw included plating media at 4 ºC, warm to 37ºC prior to thawing cells.
3. Thaw cells rapidly by removing from liquid nitrogen and immediately immersing in a 37ºC water bath. Immediately after ice has thawed, sterilize the exterior of the vial with 70% ethanol.
4. Add 1mL of pre-warmed culture media to vial. Place contents from the vial into a 15 mL conical tube and bring the volume to 9 mL with culture media.
5. Centrifuge the cell suspension at 190 x g for six minutes
6. Remove supernatant and add 10.5 mL of pre-warmed culture media to resuspend the cell pellet.
7. Seed cell suspension into black Poly-D-Lysine (clear bottom) plate (100 µL/well for 96-well plate, 25 µL/well for 384-well plate).
8. When seeding is complete, place the assay plate at room temperature for 30 minutes.
9. Move assay plate to a humidified 37ºC 5% CO_2 incubator for 18-24 hours.
10. Prepare Fluo-8 NW (AAT Bioquest 21080) Ca^{2+} dye by dissolving 1mg of Fluo-8 NW in 200 µL of DMSO. Once dissolved place 10 µL of Fluo-8 NW Ca^{2+} dye solution into 10 mL of HBSS 20mM HEPES, 2.5mM Probenecid pH 7.4 buffer and apply to assay microplate (Ca^{2+} dye at 10 µL /10 mL is sufficient for loading one (1) microplate).
11. After 24 hour incubation, remove assay plate from the incubator and wash sufficiently with Hank's Balanced Salt Solution (HBSS) supplemented with 20mM HEPES at pH 7.4 to remove all trace of Media Component, flick out remaining buffer.
12. Add 1x loading buffer to assay plate (100 µL/well for 96-well plate, 40 µL/well for 384-well plate) and incubate plate for 4 hrs at room temperature, protected from light.
13. Set-up FLIPR to dispense 3x ligand to appropriate wells in the assay plate. Set excitation wavelength at 470-495 nm (FLIPR^{TETRA}) or 485 nm (FLIPR1, FLIPR2, FLIPR3) and emission wavelength at 515-565 nm (FLIPR^{TETRA}) or emission filter for Ca^{2+} dyes (FLIPR1, FLIPR2, FLIPR3). Set pipet tip height to 5 µL below liquid level and dispense rate to 75 µL/sec (96-well format) or 50 µL/sec (384-well format). Set up plate layout and tip layout for each individual experiment. Set time course for 180 seconds, with ligand addition at 10 seconds.
14. Ligands are prepared in non-binding surface Corning plates (Corning 3605 – 96-well or Corning 3574 – 384-well).
15. After the run is complete, negative control correction is applied and data analyzed utilizing the maximum statistic.

ASSAY SETUP— cAMP

1. Immediately upon receipt, thaw cells or place cells in liquid nitrogen.
2. Thaw included plating media at 4 ºC, warm to 37ºC prior to thawing cells.
3. Thaw cells rapidly by removing from liquid nitrogen and immediately immersing in a 37ºC water bath. Immediately after ice has thawed, sterilize the exterior of the vial with 70% ethanol.
4. Add 1mL of pre-warmed culture media to vial. Place contents from the vial into a 15 mL conical tube and bring the volume to 5 mL with culture media.
5. Centrifuge the cell suspension at 190 x g for six minutes
6. Remove supernatant and add 20 mL of pre-warmed culture media to resuspend the cell pellet.
7. Seed cell suspension into white, opaque tissue-culture treated plate (Corning Costar Cat# 3917) at 100µl/well.
8. Move assay plate to a humidified 37ºC 5% CO_2 incubator for 18-24 hours.
9. On the day of assay, prepare ligands in a non-binding plate and set up assay in accordance with preferred manufacturer's cAMP kit. Read at Ex: 330nM; Em: 620nM and 665nM.

ASSAY MATERIALS

Description	Supplier and Product Number
HBSS	Hyclone: SH30268.02
HEPES 1M Stock	EMD Millipore.: TMS-003-C
Probenicid	Sigma: P8761
Quest Fluo-8™, AM	AAT Bioquest: 21080
FSH ligand	Sigma: D8040
Non-binding white plates (for ligand prep)	Corning: 3605(96-well)/3574(384-well)
Black (clear bottom) tissue-culture treated plates	Corning: 3904(96-well)/3712(384-well)

FLIPR SETTINGS

Settings for FLIPR^{TETRA}® with ICCD camera option

Option	Setting
Read Mode	Fluorescence
Ex/Em	Ex470_495 / Em515_575
Camera Gain	2000
Gate Open	6 %
Exposure Time	0.53
Read Interval	1s
Dispense Volume	50 µl (25 µl for 384-well)
Dispense Height	25 µl (50 µl for 384-well)
Dispense Speed	75 µl L/sec (50 µl for 384-well)
Expel Volume	0 µl
Analysis	Subtract Bias Sample 1

HOST CELL

HEK293

EXONGENOUS GENE EXPRESSION

Human FSHR cDNA (Accession Number: AY429104; see CODING SEQUENCE below) and a proprietary mutant clytin photoprotein and promiscuous G protein expressed in a bicistronic vector.

CODING SEQUENCE

```
ATG GCC CTG CTC CTG GTC TCT TTG CTG GCA TTC CTG AGC TTG GGC TCA GGA TGT CAT CAT CGG ATC
M   A   L   L   L   V   S   L   L   A   F   L   S   L   G   S   G   C   H   H   R   I

TGT CAC TGC TCT AAC AGG GTT TTT CTC TGC CAA GAG AGC AAG GTG ACA GAG ATT CCT TCT GAC CTC
C   H   C   S   N   R   V   F   L   C   Q   E   S   K   V   T   E   I   P   S   D   L

CCG AGG AAT GCC ATT GAA CTG AGG TTT GTC CTC ACC AAG CTT CGA GTC ATC CAA AAA GGT GCA TTT
P   R   N   A   I   E   L   R   F   V   L   T   K   L   R   V   I   Q   K   G   A   F

TCA GGA TTT GGG GAC CTG GAG AAA ATA GAG ATC TCT CAG AAT GAT GTC TTG GAG GTG ATA GAG GCA
S   G   F   G   D   L   E   K   I   E   I   S   Q   N   D   V   L   E   V   I   E   A

GAT GTG TTC TCC AAC CTT CCC AAA TTA CAT GAA ATT AGA ATT GAA AAG GCC AAC AAC CTG CTC TAC
D   V   F   S   N   L   P   K   L   H   E   I   R   I   E   K   A   N   N   L   L   Y

ATC AAC CCT GAG GCC TTC CAG AAC CTT CCC AAC CTT CAA TAT CTG TTA ATA TCC AAC ACA GGT ATT
I   N   P   E   A   F   Q   N   L   P   N   L   Q   Y   L   L   I   S   N   T   G   I

AAG CAC CTT CCA GAT GTT CAC AAG ATT CAT TCT CTC CAA AAA GTT TTA CTT GAC ATT CAA GAT AAC
K   H   L   P   D   V   H   K   I   H   S   L   Q   K   V   L   L   D   I   Q   D   N

ATA AAC ATC CAC ACA ATT GAA AGA AAT TCT TTC GTG GGG CTG AGC TTT GAA AGT GTG ATT CTA TGG
I   N   I   H   T   I   E   R   N   S   F   V   G   L   S   F   E   S   V   I   L   W

CTG AAT AAG AAT GGG ATT CAA GAA ATA CAC AAC TGT GCA TTC AAT GGA ACC CAA CTA GAT GAG CTG
L   N   K   N   G   I   Q   E   I   H   N   C   A   F   N   G   T   Q   L   D   E   L

AAT CTA AGC GAT AAT AAT AAT TTA GAA GAA TTG CCT AAT GAT GTT TTC CAC GGA GCC TCT GGA CCA
N   L   S   D   N   N   N   L   E   E   L   P   N   D   V   F   H   G   A   S   G   P

GTC ATT CTA GAT ATT TCA AGA ACA AGG ATC CAT TCC CTG CCT AGC TAT GGC TTA GAA AAT CTT AAG
V   I   L   D   I   S   R   T   R   I   H   S   L   P   S   Y   G   L   E   N   L   K

AAG CTG AGG GCC AGG TCG ACT TAC AAC TTA AAA AAG CTG CCT ACT CTG GAA AAG CTT GTC GCC CTC
K   K   L   R   A   R   S   T   Y   N   L   K   K   L   P   T   L   E   K   L   V   A

ATG GAA GCC AGC CTC ACC TAT CCC AGC CAT TGC TGT GCC TTT GCA AAC TGG AGA CGG CAA ATC TCT
M   E   A   S   L   T   Y   P   S   H   C   C   A   F   A   N   W   R   R   Q   I   S

GAG CTT CAT CCA ATT TGC AAC AAA TCT ATT TTA AGG CAA GAA GTT GAT TAT ATG ACT CAG ACT AGG
E   L   H   P   I   C   N   K   S   I   L   R   Q   E   V   D   Y   M   T   R   T   R

GGT CAG AGA TCC TCT CTG GCA GAA GAC AAT GAG TCC AGC TAC AGC AGA GGA TTT GAC ATG ACG TAC
G   Q   R   S   S   L   A   E   D   N   E   S   S   Y   S   R   G   F   D   M   T   Y

ACT GAG TTT GAC TAT GAC TTA TGC AAT GAA GTG GTT GAC GTG ACC TGC TCC CCT AAG CCA GAT GCA
T   E   F   D   Y   D   L   C   N   E   V   V   D   V   T   C   S   P   K   P   D   A

TTC AAC CCA TGT GAA GAT ATC ATG GGG TAC AAC ATC CTC AGA GTC CTG ATA TGG TTT ATC AGC ATC
F   N   P   C   E   D   I   M   G   Y   N   I   L   R   V   L   I   W   F   I   S   I

CTG GCC ATC ACT GGG AAC ATC ATA GTG CTA GTG ATC CTA ACT ACC AGC CAA TAT AAA CTC ACA GTC
L   A   I   T   G   N   I   I   V   L   V   I   L   T   T   S   Q   Y   K   L   T   V

CCC AGG TTC CTT ATG TGC AAC CTG GCC TTT GCT GAT CTC TGC ATT GGA ATC TAC CTG CTG CTC ATT
P   R   F   L   M   C   N   L   A   F   A   D   L   C   I   G   I   Y   L   L   L   I

GCA TCA GTT GAT ATC CAT ACC AAG AGC CAA TAT CAC AAC TAT GCC ATT GAC TGG CAA ACT GGG GCA
A   S   V   D   I   H   T   K   S   Q   Y   H   N   Y   A   I   D   W   Q   T   G   A

GGC TGT GAT GCT GCT GGC TTT TTC ACT GTC TTT GCC AGT GAG CTG TCA GTC TAC ACT CTG ACA GCT
G   C   D   A   A   G   F   F   T   V   F   A   S   E   L   S   V   Y   T   L   T   A

ATC ACC TTG GAA AGA TGG CAT ACC ATC ACG CAT GCC ATG CAG CTG GAC TGC AAG GTG CAG CTC CGC
I   T   L   E   R   W   H   T   I   T   H   A   M   Q   L   D   C   K   V   Q   L   R
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GGC ATC AGC AGC TAC ATG AAG GTG AGC ATC TGC CTG CCC ATG GAT ATT GAC AGC CCT TTG TCA CAG
G   I   S   S   Y   M   K   V   S   I   C   L   P   M   D   I   D   S   P   L   S   Q

CTG TAT GTC ATG TCC CTC CTT GTG CTC AAT GTC CTG GCC TTT GTG GTC ATC TGT GGC TGC TAT ATC
L   Y   V   M   S   L   L   V   L   N   V   L   A   F   V   V   I   C   G   C   Y   I

CAC ATC TAC CTC ACA GTG CGG AAC CCC AAC ATC GTG TCC TCC TCT AGT GAC ACC AGG ATC GCC AAG
H   I   Y   L   T   V   R   N   P   N   I   V   S   S   S   S   D   T   R   I   A   K

CGC ATG GCC ATG CTC ATC TTC ACT GAC TTC CTC TGC ATG GCA CCC ATT TCT TTC TTT GCC ATT TCT
R   M   A   M   L   I   F   T   D   F   L   C   M   A   P   I   S   F   F   A   I   S

GCC TCC CTC AAG GTG CCC CTC ATC ACT GTG TCC AAA GCA AAG ATT CTG CTG GTT CTG TTT CAC CCC
A   S   L   K   V   P   L   I   T   V   S   K   A   K   I   L   L   V   L   F   H   P

ATC AAC TCC TGT GCC AAC CCC TTC CTC TAT GCC ATC TTT ACC AAA AAC TTT CGC AGA GAT TTC TTC
I   N   S   C   A   N   P   F   L   Y   A   I   F   T   K   N   F   R   R   D   F   F

ATT CTG CTG AGC AAG TGT GGC TGC TAT GAA ATG CAA GCC CAA ATT TAT AGG ACA GAA ACT TCA TCC
I   L   L   S   K   C   G   C   Y   E   M   Q   A   Q   I   Y   R   T   E   T   S   S

ACT GTC CAC AAC ACC CAT CCA AGG AAT GGC CAC TGC TCT TCA GCT CCC AGA GTC ACC AAT GGT TCC
T   V   H   N   T   H   P   R   N   G   H   C   S   S   A   P   R   V   T   N   G   S

ACT TAC ATA CTT GTC CCT CTA AGT CAT TTA GCC CAA AAC TAA
 T   Y   I   L   V   P   L   S   H   L   A   Q   N  Stp
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RELATED PRODUCTS

PRODUCT NUMBER	DESCRIPTION
HTS233LRTA	ChemiBrite™ LH Glycoprotein Receptor Frozen Cells

REFERENCES

1. Simoni, M. *et al.* (1997) The Follicle-Stimulating Hormone: Biochemistry, Molecular Biology, Physiology, and Pathophysiology. *Endocrine Review* 18(6): 739-773.
2. Verrier, B et al. (1977) Thyrotropin Binding to and Adenylate Cyclase Activity of Porcine Thyroid Plasma Membranes. *Eur J Biochem* 74, 243-252.

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