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Yang et al.

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(45) **Date of Patent: Feb. 14, 2023**

(54) **HIPPO PATHWAY BIOLUMINESCENT BIOSENSOR**

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(73) Assignee: **Queen's University at Kingston**, Kingston (CA)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 649 days.

(21) Appl. No.: **16/177,691**

(22) Filed: **Nov. 1, 2018**

(65) **Prior Publication Data**

US 2019/0256887 A1 Aug. 22, 2019

Related U.S. Application Data

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(51) **Int. Cl.**

C12Q 1/66	(2006.01)
G01N 33/58	(2006.01)
C07K 14/47	(2006.01)
C07K 14/435	(2006.01)
C12N 9/02	(2006.01)

(52) **U.S. Cl.**

CPC ***G01N 33/582*** (2013.01); ***C07K 14/4702*** (2013.01); ***C12Q 1/66*** (2013.01); *C07K 14/43563* (2013.01); *C07K 2319/61* (2013.01); *C07K 2319/71* (2013.01); *C12N 9/0069* (2013.01); *C12Y 113/12013* (2013.01)

(58) **Field of Classification Search**

CPC C12Q 1/66; C12Y 13/12013

See application file for complete search history.

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Zhao, B. et al., "TEAD mediates YAP-dependent gene induction and growth control", Genes Dev. 22, pp. 1962-1971 (2008).
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Primary Examiner — Karen Cochrane Carlson
(74) *Attorney, Agent, or Firm* — Stephen J. Scribner

(57) **ABSTRACT**

Bioluminescent biosensors useful for monitoring and/or quantifying, in vitro or in vivo, activity of the Hippo signaling pathway. The biosensors monitor LATS kinase activity or YAP-TEAD interaction. The biosensors may be used in methods for monitoring and/or quantifying in real-time, in vitro or in vivo, activity of the Hippo signaling pathway, wherein the activity may be LATS kinase activity and/or YAP-TEAD interaction. The biosensors may be provided in kits for monitoring and/or quantifying in real-time, in vitro or in vivo, activity of the Hippo signaling pathway, wherein the activity may be LATS kinase activity and/or YAP-TEAD interaction.

14 Claims, 19 Drawing Sheets

Specification includes a Sequence Listing.

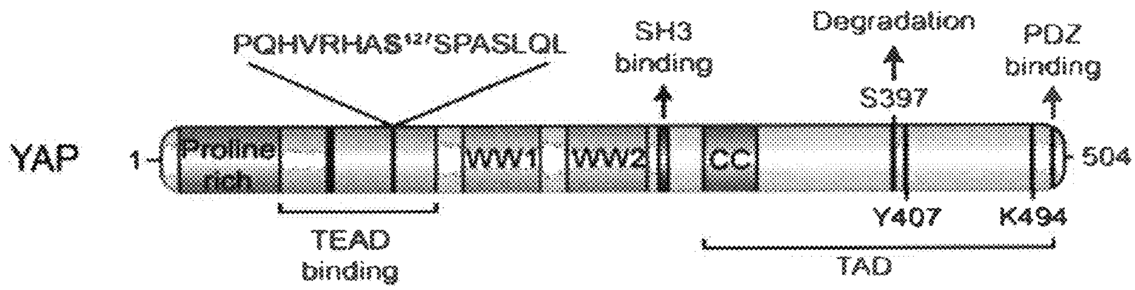

PQHVRHAS127SPASLQL
SH3 binding
Degradation
PDZ binding
S397
YAP
1
Proline rich
WW1
WW2
CC
504
Y407
K494
TEAD binding
TAD

Fig. 1A

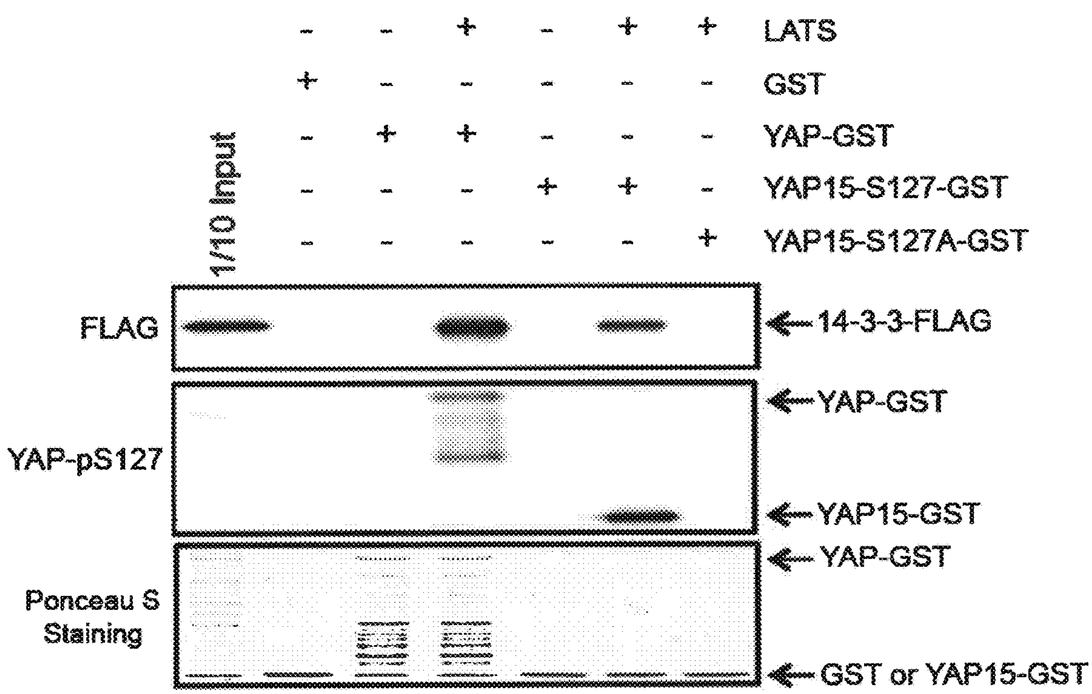

LATS
GST
YAP-GST
YAP15-S127-GST
YAP15-S127A-GST
1/10 Input
FLAG
14-3-3-FLAG
YAP-pS127
YAP-GST
YAP15-GST
Ponceau S Staining
YAP-GST
GST or YAP15-GST

Fig. 1B

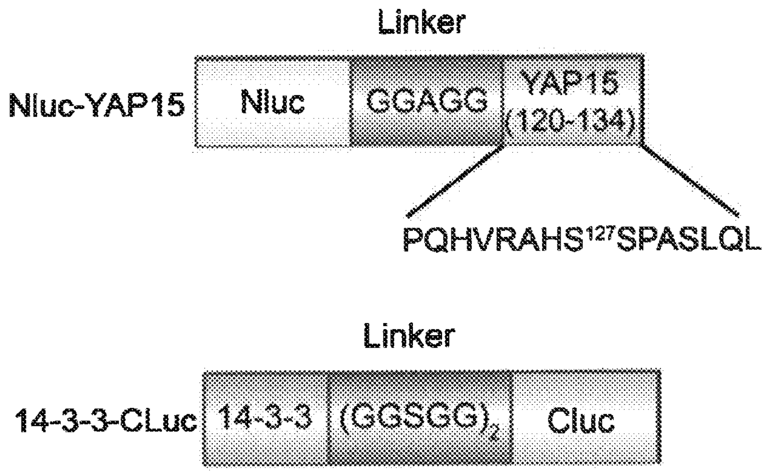

Linker
Nluc-YAP15
Nluc
GGAGG
YAP15 (120-134)
PQHVRAHS127SPASLQL
Linker
14-3-3-CLuc
14-3-3
(GGSGG)2
Cluc

Fig. 2A

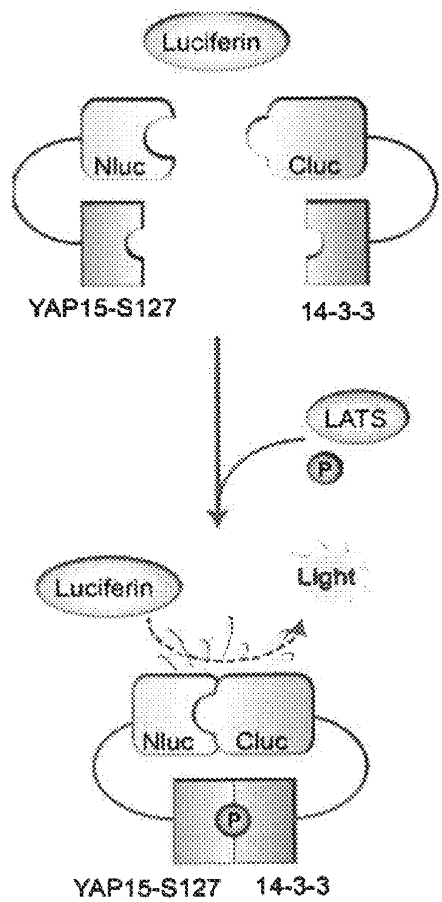
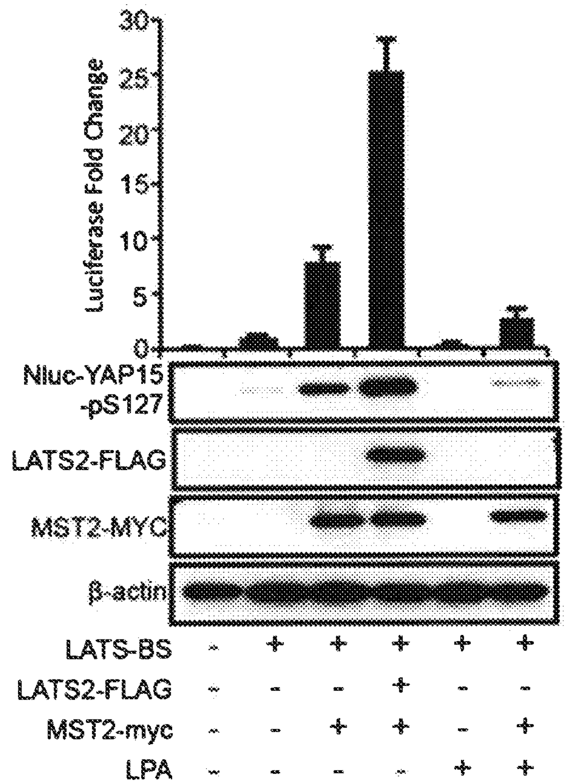
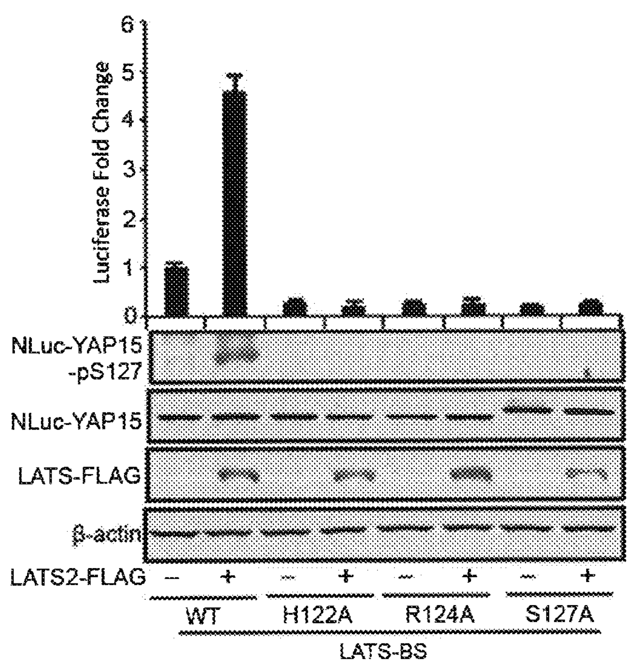

Luciferin
Nluc
Cluc
YAP15-S127
14-3-3
LATS
P
Luciferin
Light
Nluc
Cluc
P
YAP15-S127
14-3-3

Fig. 2B



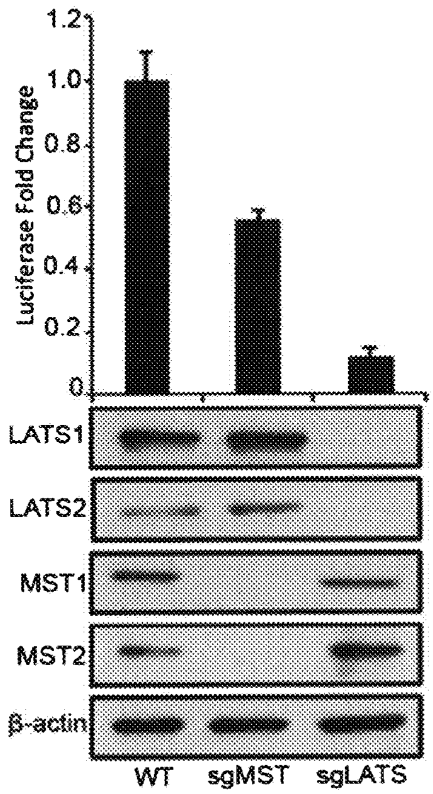
Luciferase Fold Change
30
25
20
15
10
5
0
Nluc-YAP15
-pS127
LATS2-FLAG
MST2-MYC
β-actin
LATS-BS - + + + + +
LATS2-FLAG - - - + - -
MST2-myc - - + + - +
LPA - - - - + +

Fig. 2C



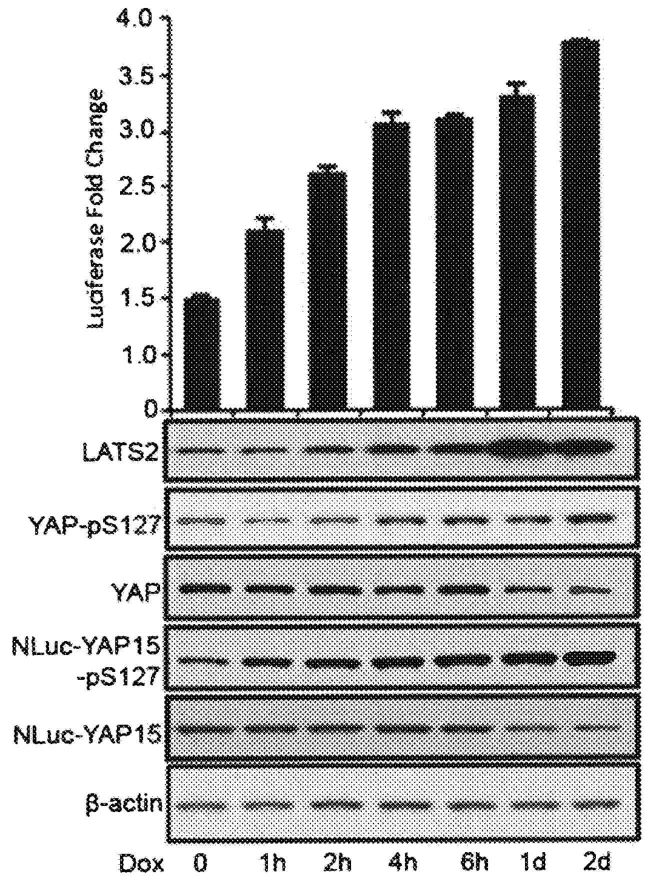
Luciferase Fold Change
6
5
4
3
2
1
0
NLuc-YAP15
-pS127
NLuc-YAP15
LATS-FLAG
β-actin
LATS2-FLAG – + – + – + – +
WT
H122A
R124A
S127A
LATS-BS

Fig. 2D



1.2
1.0
0.8
0.6
0.4
0.2
0
Luciferase Fold Change
LATS1
LATS2
MST1
MST2
β-actin
WT
sgMST
sgLATS

Fig. 2E



4.0
3.5
3.0
2.5
2.0
1.5
1.0
0
Luciferase Fold Change
LATS2
YAP-pS127
YAP
NLuc-YAP15
-pS127
NLuc-YAP15
β-actin
Dox
0
1h
2h
4h
6h
1d
2d

Fig. 2F

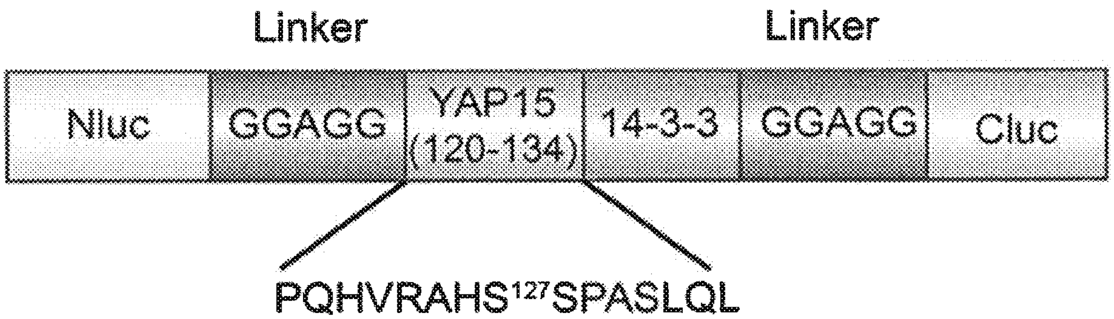

Linker
Linker
Nluc
GGAGG
YAP15 (120-134)
14-3-3
GGAGG
Cluc
PQHVRAHS127SPASLQL

Fig. 3A

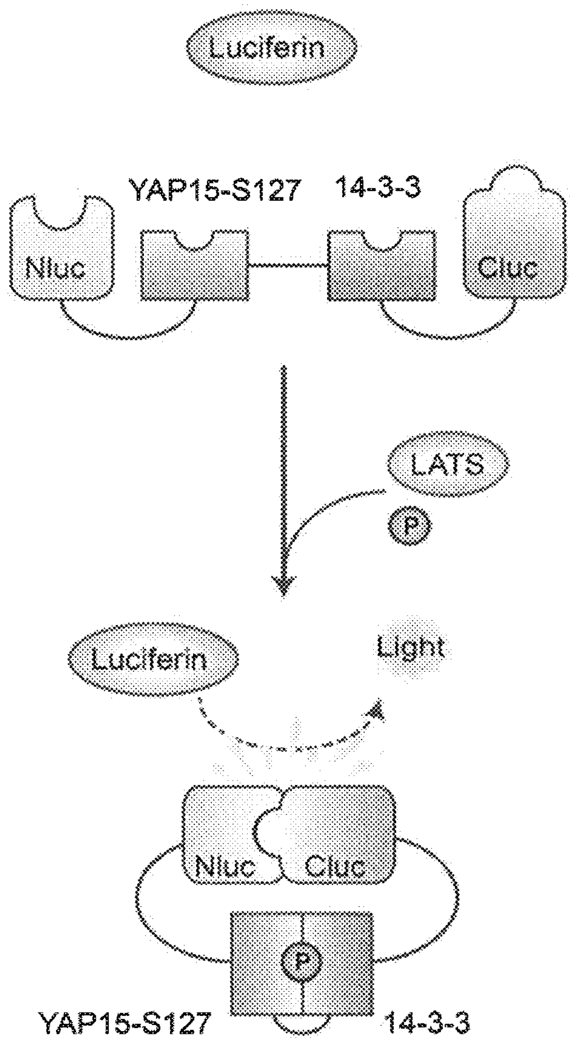

Luciferin
YAP15-S127
14-3-3
Nluc
Cluc
LATS
P
Luciferin
Light
Nluc
Cluc
P
YAP15-S127
14-3-3

Fig. 3B

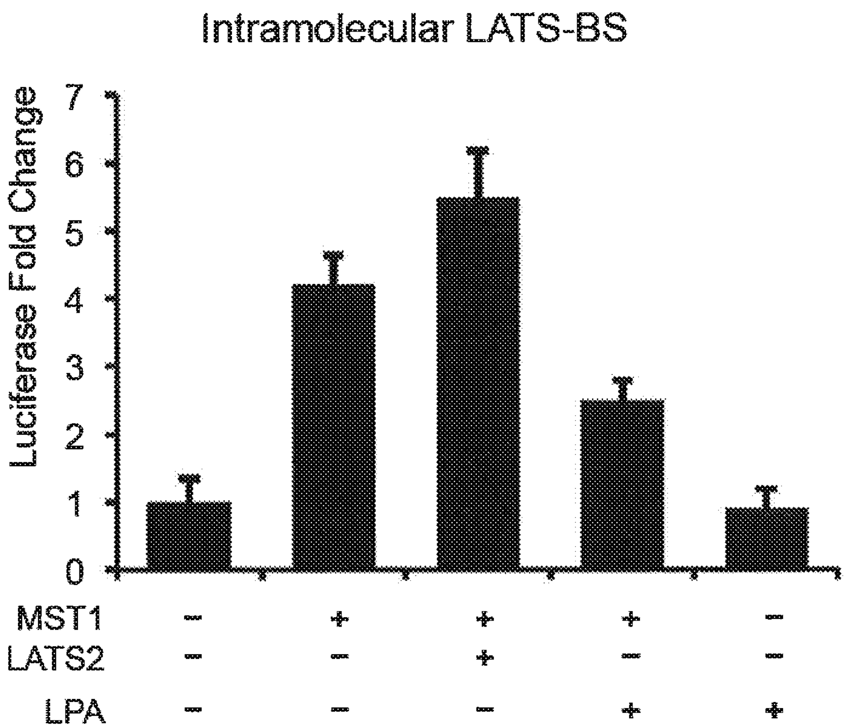

Intramolecular LATS-BS
Luciferase Fold Change
0
1
2
3
4
5
6
7
MST1 − + + + −
LATS2 − − + − −
LPA − − − + +

Fig. 3C

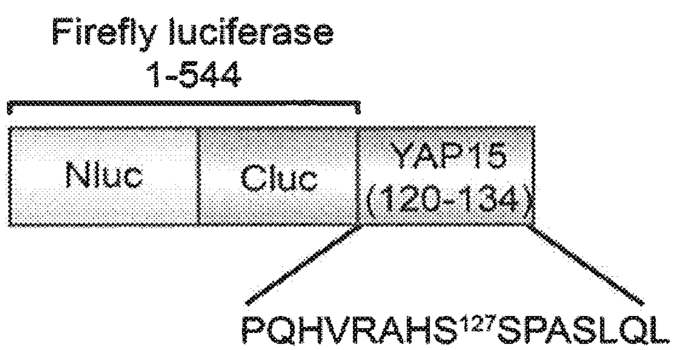

Firefly luciferase
1-544
Nluc
Cluc
YAP15
(120-134)
PQHVRAHS127SPASLQL

Fig. 4A

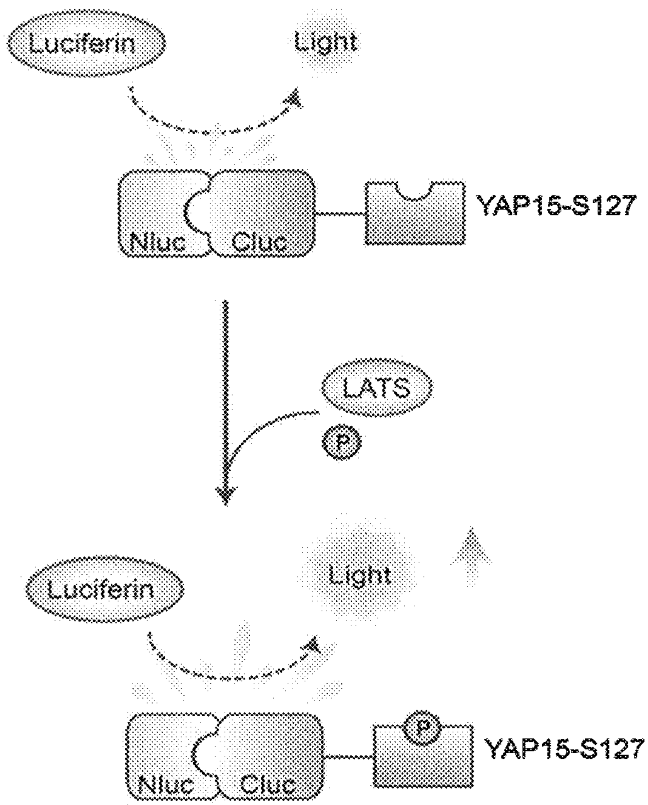

Luciferin
Light
Nluc
Cluc
YAP15-S127
LATS
P
Luciferin
Light
Nluc
Cluc
P
YAP15-S127

Fig. 4B

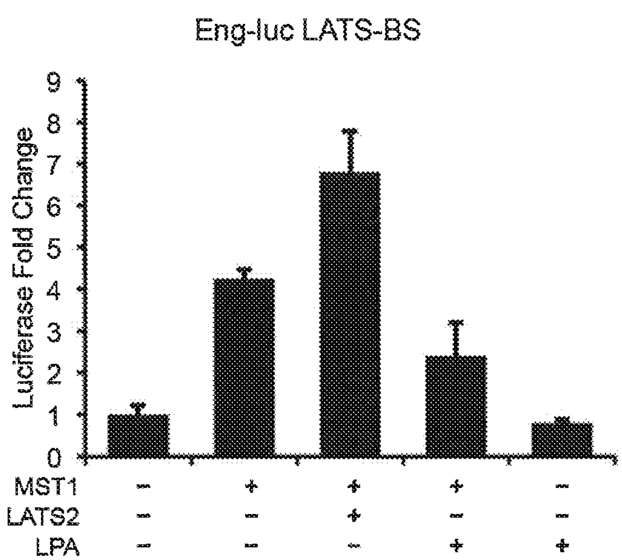

Eng-luc LATS-BS
Luciferase Fold Change
0
1
2
3
4
5
6
7
8
9
MST1 − + + + −
LATS2 − − + − −
LPA − − − + +

Fig. 4C

Fig. 5A

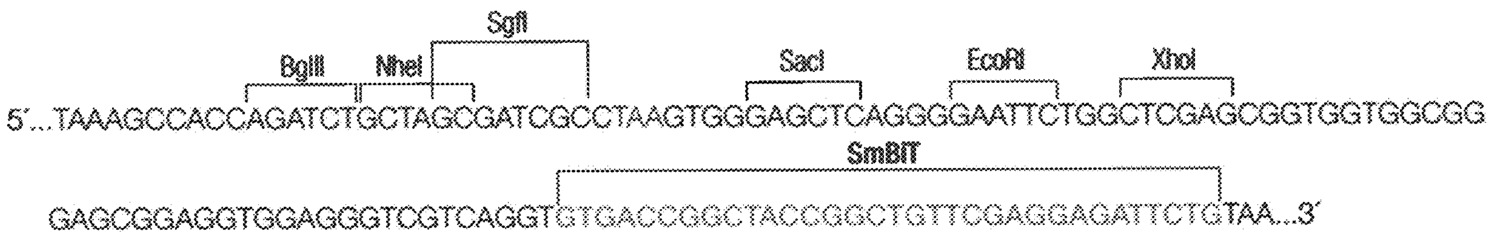


Fig. 5B

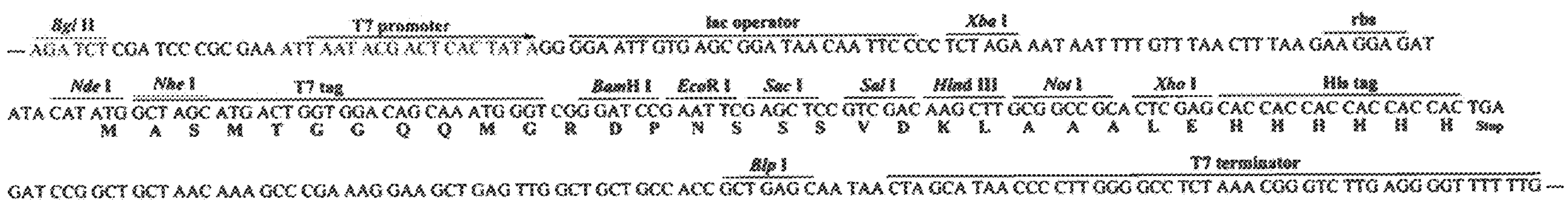


Fig. 5C

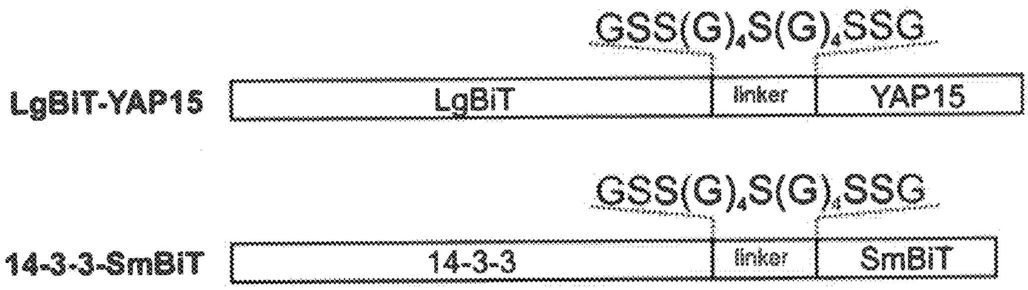

GSS(G)4S(G)4SSG
LgBiT-YAP15
LgBiT
linker
YAP15
GSS(G)4S(G)4SSG
14-3-3-SmBiT
14-3-3
linker
SmBiT

Fig. 5D

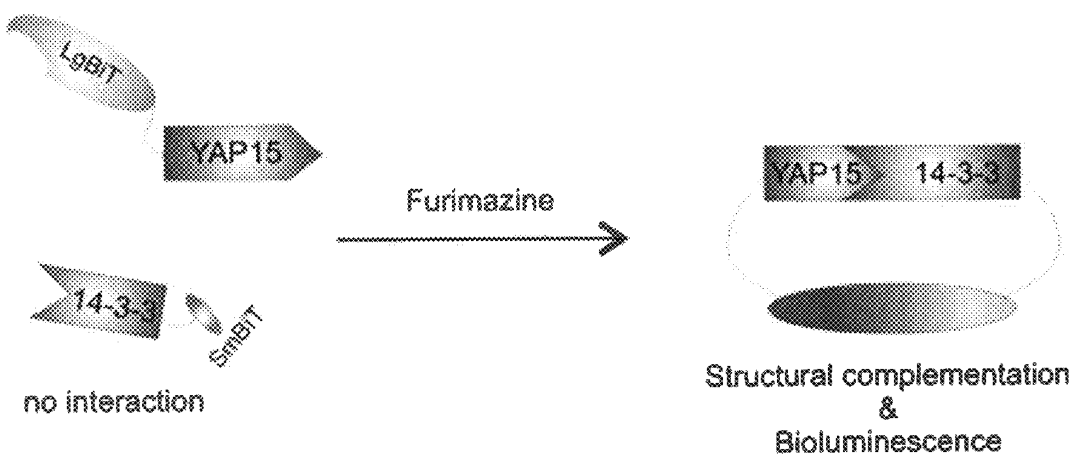
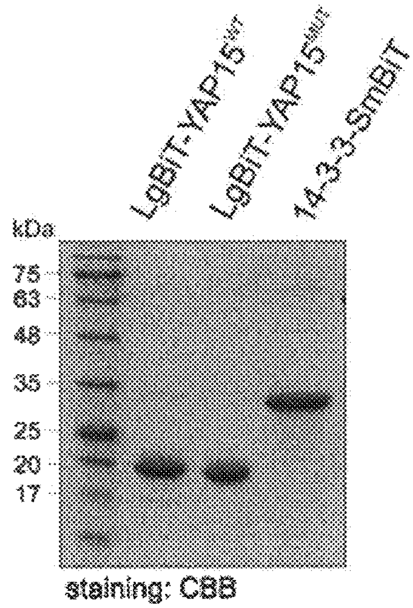
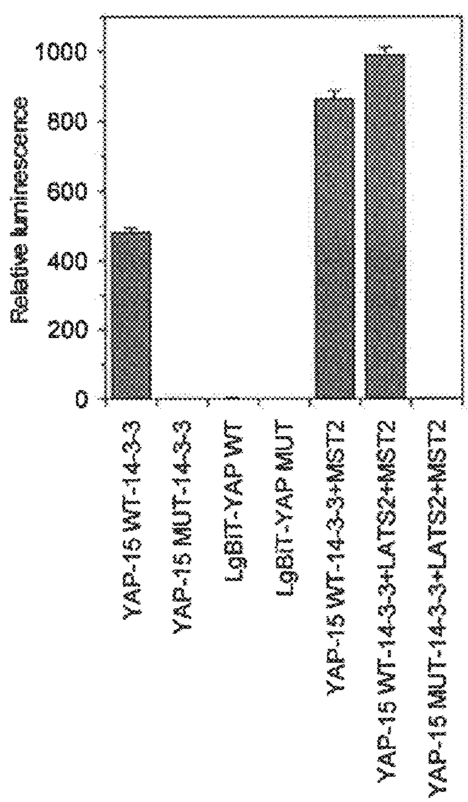

LgBiT
YAP15
14-3-3
SmBiT
no interaction
Furimazine
YAP15
14-3-3
Structural complementation
&
Bioluminescence

Fig. 6



LgBiT-YAP15WT
LgBiT-YAP15MUT
14-3-3-SmBiT
kDa
75
63
48
35
25
20
17
staining: CBB

Fig. 7



Relative luminescence
1000
800
600
400
200
0
YAP-15 WT-14-3-3
YAP-15 MUT-14-3-3
LgBiT-YAP WT
LgBiT-YAP MUT
YAP-15 WT-14-3-3+MST2
YAP-15 WT-14-3-3+LATS2+MST2
YAP-15 MUT-14-3-3+LATS2+MST2

Fig. 8A

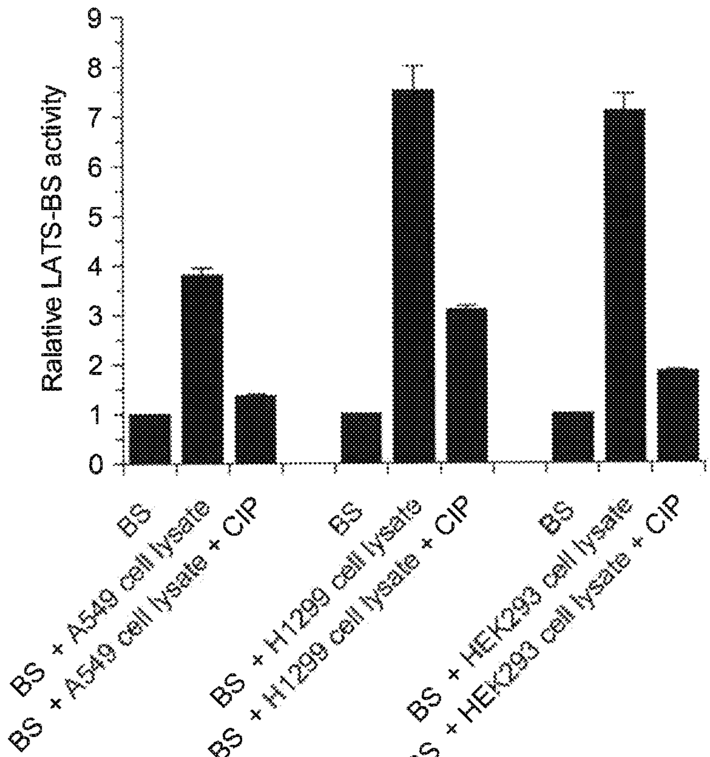

Ralative LATS-BS activity
9
8
7
6
5
4
3
2
1
0
BS
BS + A549 cell lysate
BS + A549 cell lysate + CIP
BS
BS + H1299 cell lysate
BS + H1299 cell lysate + CIP
BS
BS + HEK293 cell lysate
BS + HEK293 cell lysate + CIP

Fig. 8B

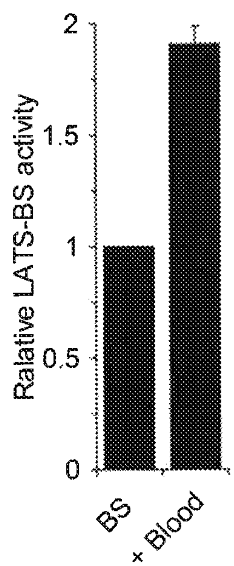
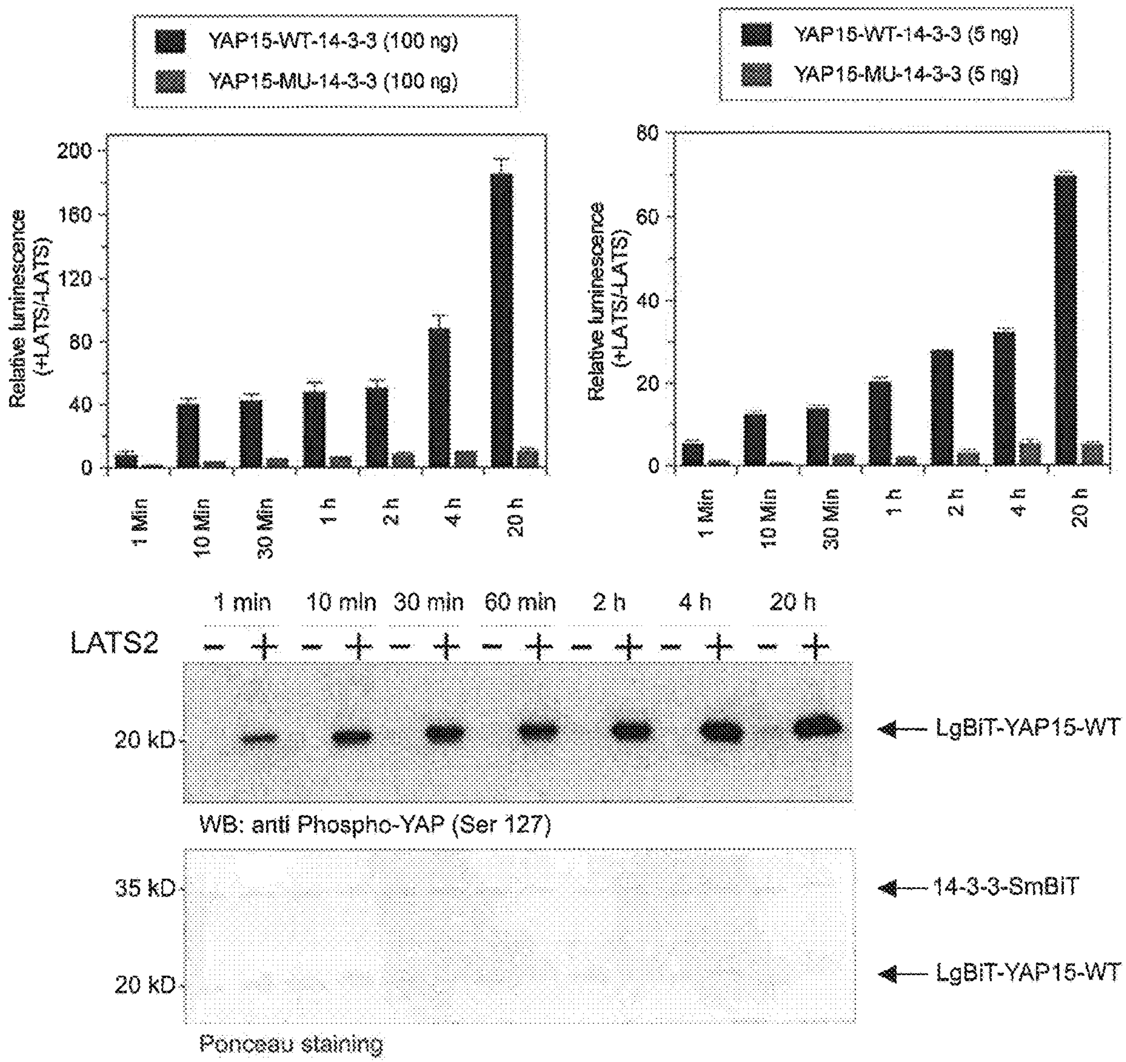
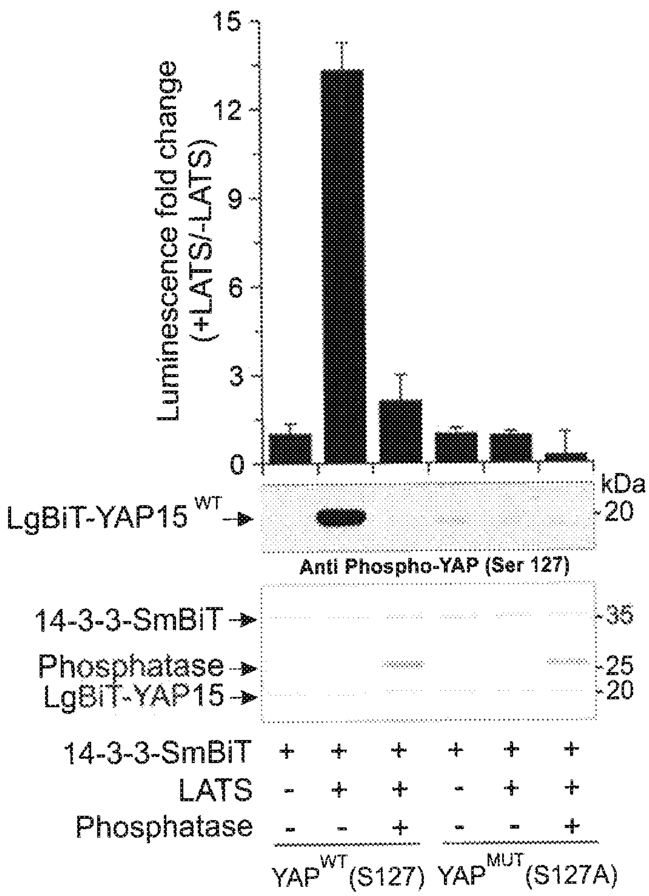

Ralative LATS-BS activity
2
1.5
1
0.5
0
BS
BS + Blood

Fig. 8C



YAP15-WT-14-3-3 (100 ng)
YAP15-MU-14-3-3 (100 ng)
Relative luminescence (+LATS/-LATS)
200
160
120
80
40
0
1 Min
10 Min
30 Min
1 h
2 h
4 h
20 h
YAP15-WT-14-3-3 (5 ng)
YAP15-MU-14-3-3 (5 ng)
80
60
40
20
0
1 min
10 min
30 min
60 min
2 h
4 h
20 h
LATS2
20 kD
LgBiT-YAP15-WT
WB: anti Phospho-YAP (Ser 127)
35 kD
14-3-3-SmBiT
20 kD
LgBiT-YAP15-WT
Ponceau staining

Fig. 9



15
12
9
6
3
0
Luminescence fold change
(+LATS/-LATS)
kDa
LgBiT-YAP15 WT
20
Anti Phospho-YAP (Ser 127)
14-3-3-SmBiT
35
Phosphatase
25
LgBiT-YAP15
20
14-3-3-SmBiT + + + + + +
LATS - + + - + +
Phosphatase - - + - - +
YAP WT (S127) YAP MUT (S127A)

Fig. 10

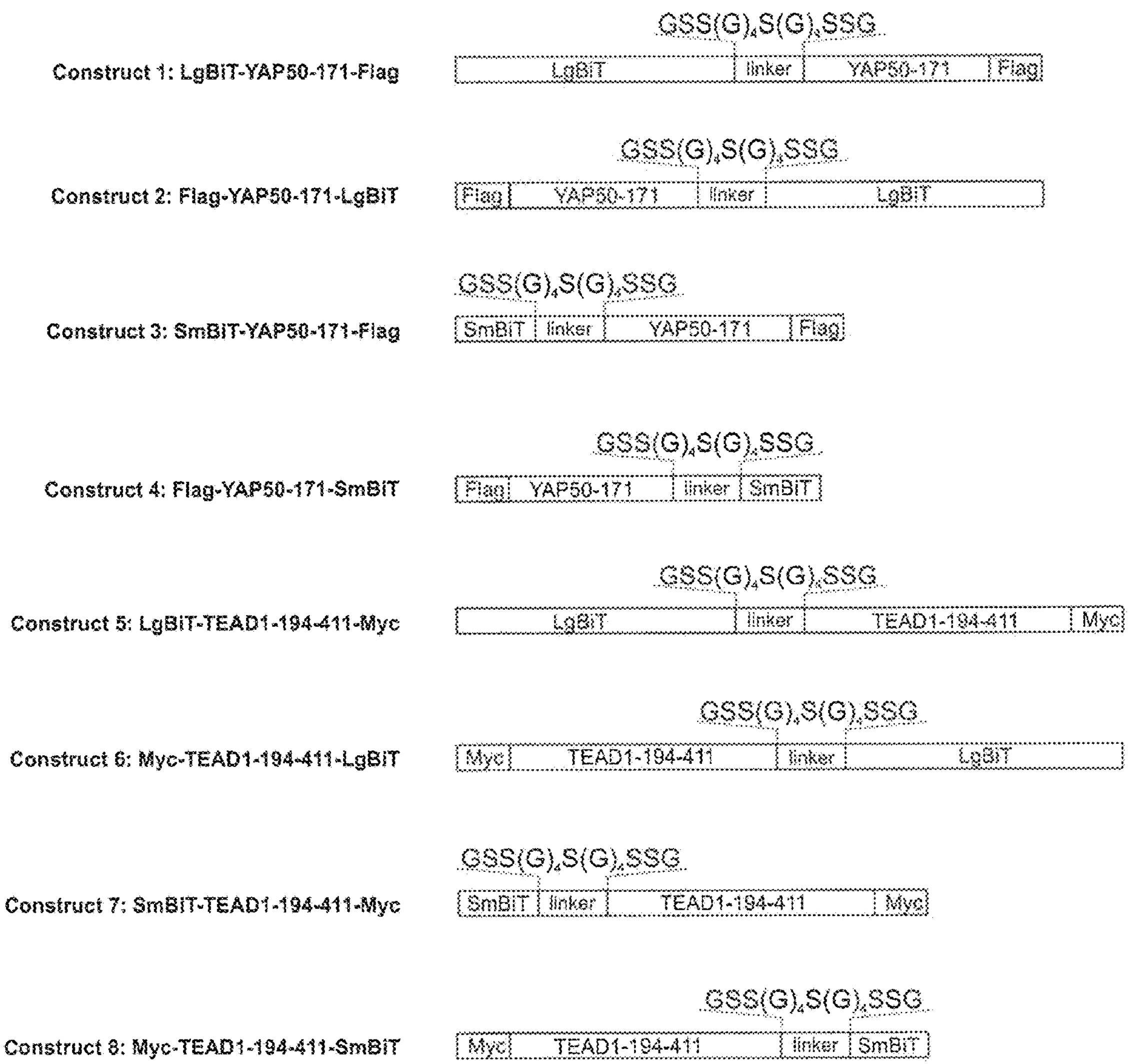

Construct 1: LgBiT-YAP50-171-Flag
GSS(G)4S(G)4SSG
LgBiT linker YAP50-171 Flag
Construct 2: Flag-YAP50-171-LgBiT
GSS(G)4S(G)4SSG
Flag YAP50-171 linker LgBiT
Construct 3: SmBiT-YAP50-171-Flag
GSS(G)4S(G)4SSG
SmBiT linker YAP50-171 Flag
Construct 4: Flag-YAP50-171-SmBiT
GSS(G)4S(G)4SSG
Flag YAP50-171 linker SmBiT
Construct 5: LgBiT-TEAD1-194-411-Myc
GSS(G)4S(G)4SSG
LgBiT linker TEAD1-194-411 Myc
Construct 6: Myc-TEAD1-194-411-LgBiT
GSS(G)4S(G)4SSG
Myc TEAD1-194-411 linker LgBiT
Construct 7: SmBiT-TEAD1-194-411-Myc
GSS(G)4S(G)4SSG
SmBiT linker TEAD1-194-411 Myc
Construct 8: Myc-TEAD1-194-411-SmBiT
GSS(G)4S(G)4SSG
Myc TEAD1-194-411 linker SmBiT

Fig. 11

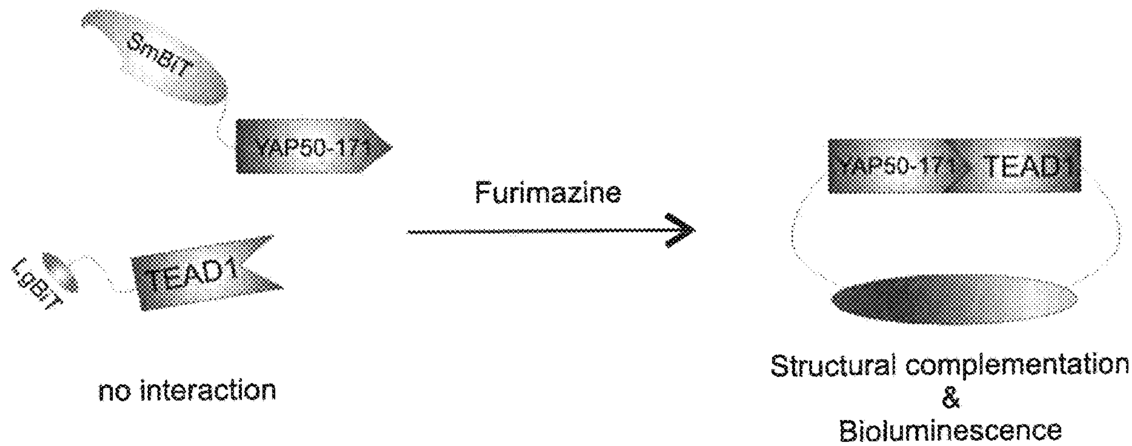

SmBiT
YAP50-171
LgBiT
TEAD1
no interaction
Furimazine
YAP50-171
TEAD1
Structural complementation
&
Bioluminescence

Fig. 12

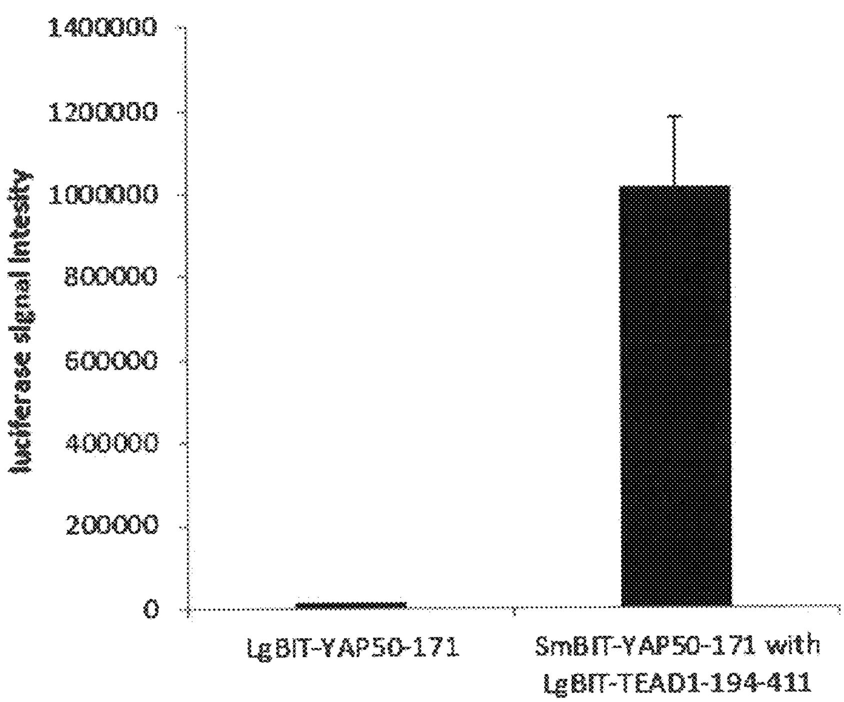
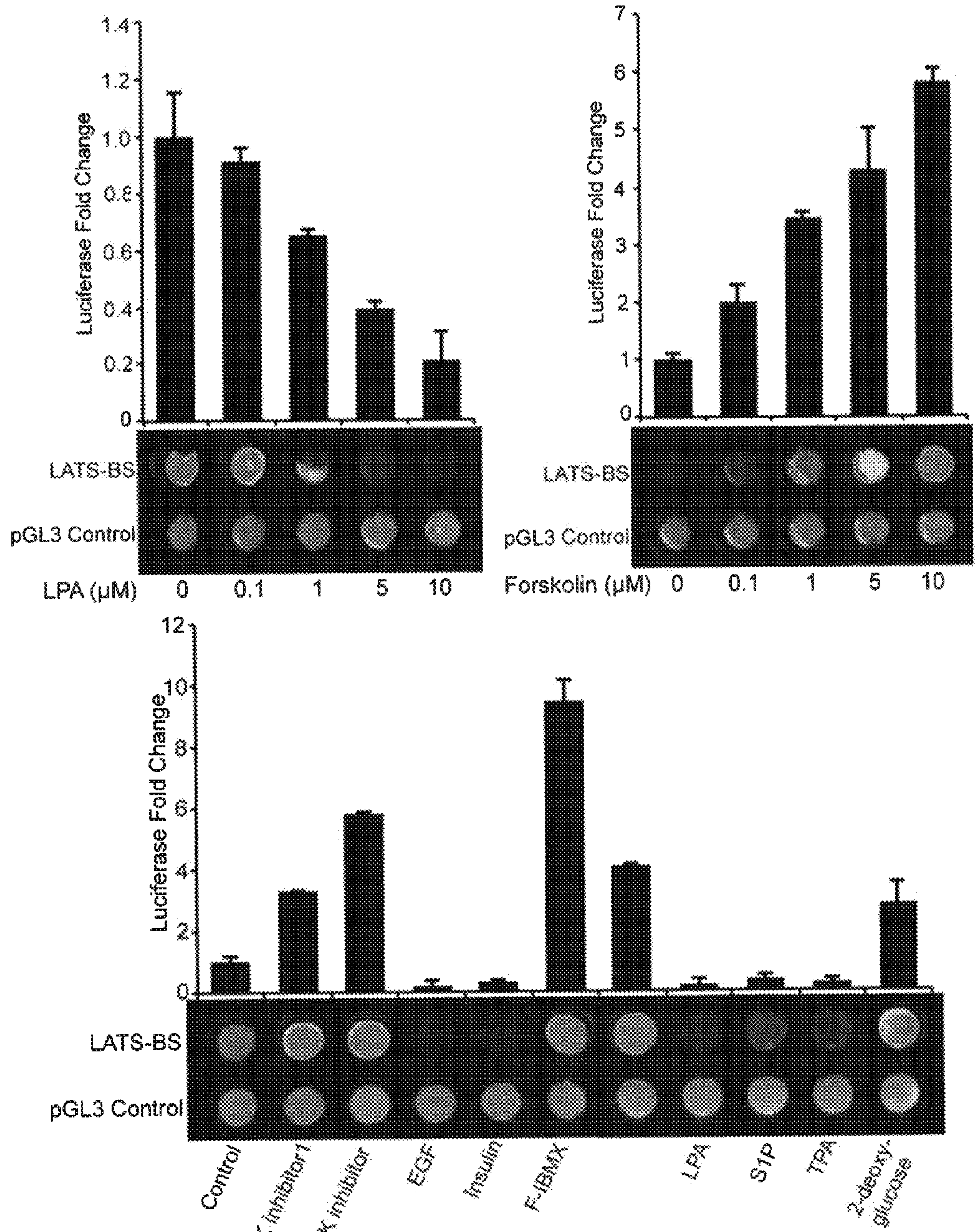

1400000
1200000
1000000
800000
600000
400000
200000
0
luciferase signal intesity
LgBIT-YAP50-171
SmBIT-YAP50-171 with
LgBIT-TEAD1-194-411

Fig. 13



1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
Luciferase Fold Change
LATS-BS
pGL3 Control
LPA (μM) 0 0.1 1 5 10
7
6
5
4
3
2
1
0
Luciferase Fold Change
LATS-BS
pGL3 Control
Forskolin (μM) 0 0.1 1 5 10
12
10
8
6
4
2
0
Luciferase Fold Change
LATS-BS
pGL3 Control
Control
PI3K inhibitor1
PDK inhibitor
EGF
Insulin
F-IBMX
LPA
S1P
TPA
2-deoxy-glucose

Fig. 14

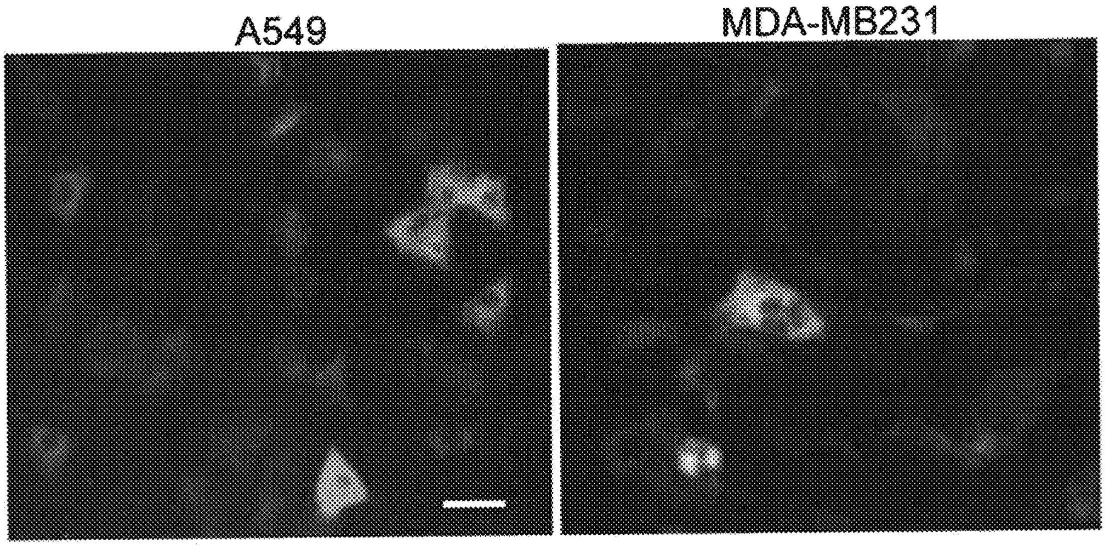


Fig. 15

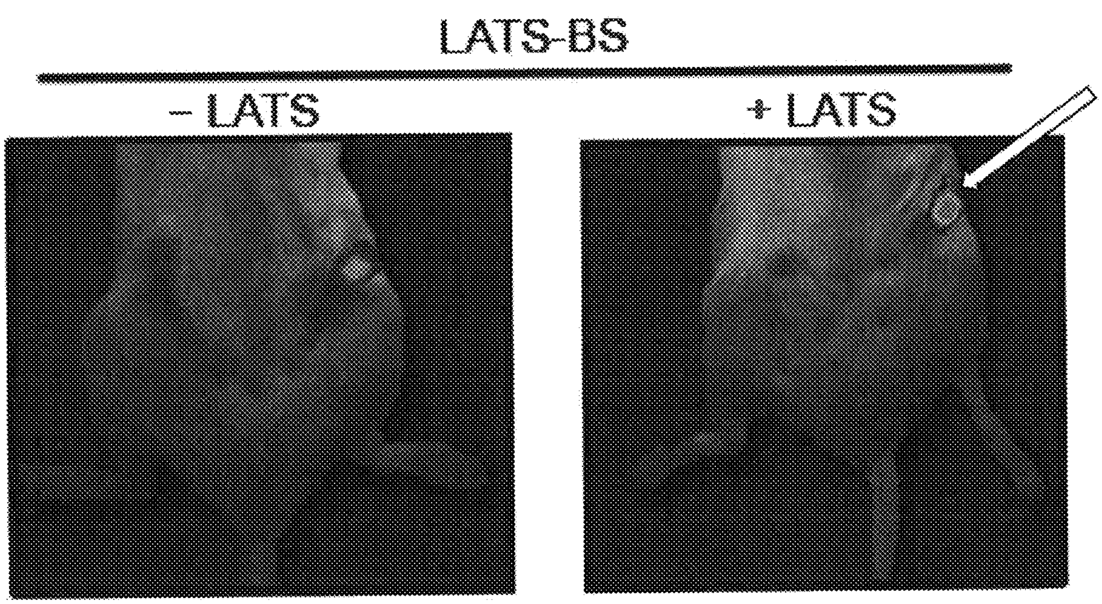


Fig. 16

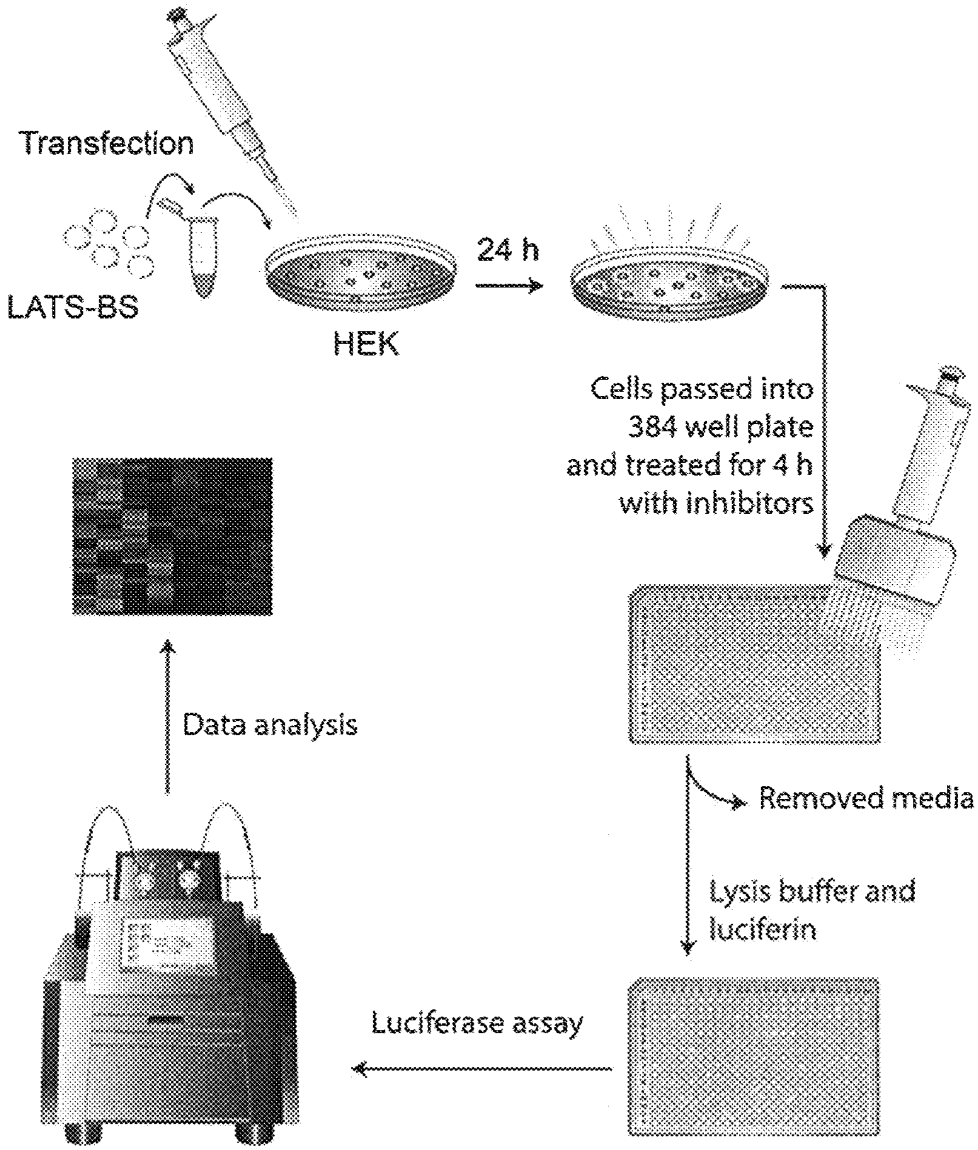

Transfection
LATS-BS
HEK
24 h
Cells passed into
384 well plate
and treated for 4 h
with inhibitors
Removed media
Lysis buffer and
luciferin
Luciferase assay
Data analysis

Fig. 17A


-23
0
+23
DMSO
SC 514
BI 78D3
Compound 401
SD 208
BIO
GSK 650394
Naphthyl PP1
SU 5416
Iressa
GW 843682X
DMSO
DMSO
FPA 124
H 89
EO 1428
D 4476
NU 7026
PI 828
PQ 401
CGP 57380
LY 364947
PD 407824
DMSO
DMSO
PHA 665752
CGK 733
IMD 0354
Ryuvidine
PD 198306
TCS 359
SB 218078
TPCA-1
DEBC
Ki 8751
DMSO
DMSO
PHA 665752
CGK 733
IMD 0354
Ryuvidine
PD 198306
TCS 359
SB 218078
TPCA-1
DEBC
Ki 8751
DMSO
DMSO
IKK 16
ZM 306416
ZM 323881
ER 27319 maleate
ZM 447439
Arcyriaflavin A
CGP 53353
BIBX 1382
HA 1100
Hexabromocyclo
DMSO
DMSO
TBB
Ro 08-2750
GW 583340
GW 441756
API-2
Aminopurvalanol
Ro 31-8220
SL 327
SB 239063
NSC 693868
DMSO
DMSO
Arctigenin
SB 415286
SB 216763
SB 431542
KU 55933
Purvalanol B
Purvalanol A
SP 600125
SU 4312
PP 2
DMSO
DMSO
Terreic acid
SB 203580
PP 1
GW 5074
ZM 39923
ZM 449829
ZM 336372
LFM-A13
Olomoucine
SB 202190
DMSO
DMSO
Y-27632
PD 98059
U0126
LY 294002
Genistein
GF 109203X
Fasudil
NH 125
ML9
AG 490
DMSO

Fig. 17B

HIPPO PATHWAY BIOLUMINESCENT BIOSENSOR

REFERENCE TO AN ELECTRONIC SEQUENCE LISTING

The contents of the electronic sequence listing (16177691sequencelistingST25-2.txt; size: 180 kB; date of creation: Aug. 19, 2022) is herein incorporated by reference in its entirety.

RELATED APPLICATION

This application claims the benefit of the filing date of Application No. 62/580,186, filed Nov. 1, 2017, the contents of which are incorporated herein by reference in their entirety.

FIELD

This invention relates to bioluminescent biosensors for non-invasively monitoring and/or quantifying in real-time, in vitro or in vivo, activity of the Hippo signaling pathway.

BACKGROUND

Detailed understanding of biochemical pathways will elucidate signaling mechanisms in physiological and pathological processes, yielding insight into approaches for controlling, treating, and preventing many diseases. The ability to gain such insight is severely limited by the complexity of such pathways and the difficulty in monitoring the activity of key components once identified.

The Hippo pathway is a signaling cascade that plays important roles in development (e.g., organ size control, 3D body shape, and early embryo development), cancer (tumorigenesis, metastasis, drug resistance, and immune evasion), regeneration medicine (stem cell renewal and differentiation and tissue homeostasis/regeneration), heart development and disease (cardiomyocyte proliferation and heart infarction/cardiac injury) and in the neuronal system (neural fate and dendrite tiling)[1-9]. Dysregulation of the Hippo pathway is frequently observed in human cancers. When Hippo signaling is activated by upstream regulators, MST1/2 serine/threonine (S/T) kinases (mammalian homologs of *Drosophila* Hippo) phosphorylate/activate LATS1/2 kinases which subsequently phosphorylate/inactivate their downstream effectors, transcriptional co-activator Yes-associated protein (YAP) and its paralog transcriptional co-activator with PDZ-binding motif (TAZ). S127-phosphorylated YAP (YAP-pS127) or S89-phosphorylated TAZ (TAZ-pS89) bind to cytoplasmic protein 14-3-3 and are prevented from binding to transcription factor TEAD to trans-activate downstream gene targets in the nucleus (e.g., CTGF, CYR61, FGF1, etc.)[10-14]. Although a few regulatory factors of the Hippo pathway have been uncovered (actin dynamics, cell matrix stiffness, cell-cell contact, and lysophosphatidic acid (LPA)[3, 6], comprehensive regulator screens have been technically limited. An absence of available tools precludes measuring the dynamics and activity of the Hippo pathway core components in a quantitative, high-throughput and non-invasive manner.

SUMMARY

One aspect of the invention relates to a luminescent biosensor, comprising: one or more fragments of firefly or NanoBiT luciferase or a functional equivalent thereof; at least one fragment of human YAP or a functional equivalent thereof; and at least one vector.

In one embodiment, the biosensor comprises: a first construct comprising an N-terminal luciferase fragment (Nluc) or a functional equivalent thereof fused to the at least one YAP fragment; a second construct comprising a C-terminal luciferase fragment (Cluc) or a functional equivalent thereof fused to human cytoplasmic 14-3-3 protein or a functional equivalent thereof; wherein the first construct and the second construct are on separate vectors; wherein LATS-dependent phosphorylation of the at least one YAP fragment leads to binding with the human cytoplasmic 14-3-3 protein, which results in binding of Nluc and Cluc to produce luminescence.

In one embodiment, the biosensor comprises Nluc luciferase amino acids 1-416 of SEQ ID NO:6 or a functional equivalent thereof; Cluc luciferase amino acids 394-550 of SEQ ID NO:6 or a functional equivalent thereof; and YAP fragment including 15 amino acids (residues 120-134; SEQ ID NO:7) or a functional equivalent thereof.

In one embodiment, the biosensor comprises a single construct including: an N-terminal luciferase fragment (Nluc) or a functional equivalent thereof fused to the at least one YAP fragment; and a C-terminal luciferase fragment (Cluc) or a functional equivalent thereof fused to human cytoplasmic 14-3-3 protein; wherein LATS-dependent phosphorylation of the at least one YAP fragment leads to a conformational change and binding of Nluc and Cluc to produce luminescence.

In one embodiment, the biosensor comprises Nluc luciferase amino acids 1-416 of SEQ ID NO:6 or a functional equivalent thereof; Cluc luciferase amino acids 394-550 of SEQ ID NO:6 or a functional equivalent thereof; and YAP fragment including 15 amino acids (residues 120-134; SEQ ID NO:7) or a functional equivalent thereof.

In one embodiment, the biosensor comprises a single construct including a luciferase engineered at the C-terminal fused to the one or more YAP fragment; wherein LATS-dependent phosphorylation of the one or more YAP fragment modulates luciferase activity to increase luminescence. In one embodiment, the luciferase is engineered at the C-terminal consisting of amino acids 1-544 (SEQ ID NO:6) or a functional equivalent thereof.

In one embodiment, the biosensor comprises a first construct comprising a LgBiT luciferase fragment or a functional equivalent thereof fused to the at least one YAP fragment or a functional equivalent thereof a second construct comprising a SmBiT luciferase fragment or a functional equivalent thereof fused to human cytoplasmic 14-3-3 protein or a functional equivalent thereof; wherein the first construct and the second construct are on separate vectors; wherein binding of the at least one YAP fragment with the human cytoplasmic 14-3-3 protein and leads to binding of LgBiT and SmBiT to produce luminescence. In one embodiment, the biosensor comprises YAP fragment including 15 amino acids (residues 120-134; SEQ ID NO:7) or a functional equivalent thereof.

In one embodiment, the biosensor comprises: a first construct comprising a LgBiT luciferase fragment or a functional equivalent thereof fused to the at least one YAP fragment or a functional equivalent thereof; a second construct comprising a SmBiT luciferase fragment or a functional equivalent thereof fused to a TEAD fragment or a functional equivalent thereof, or a first construct comprising a LgBiT luciferase fragment or a functional equivalent thereof fused to a TEAD fragment or a functional equivalent

thereof; a second construct comprising a SmBiT luciferase fragment or a functional equivalent thereof fused to the at least one YAP fragment or a functional equivalent thereof; wherein the first construct and the second construct are on separate vectors; wherein interaction of the at least one YAP fragment with the TEAD fragment leads to binding of LgBiT and SmBiT to produce luminescence.

In one embodiment, the biosensor comprises: YAP fragment comprising amino acids 50-171 of SEQ ID NO:2 or a functional equivalent thereof; and TAED fragment comprising amino acids 194-411 of SEQ ID NO:50 or a functional equivalent thereof.

Another aspect of the invention relates to a method, comprising: non-invasively monitoring and/or quantifying in real-time, in vitro or in vivo, activity of the Hippo signaling pathway, comprising transfecting a cell with a luminescent biosensor as described herein, and detecting luminescence; wherein an intensity of the luminescence is indicative of amount of activity of the Hippo signaling pathway.

Another aspect of the invention relates to a method for monitoring and/or quantifying activity of the Hippo signaling pathway, comprising: treating a cell with a luminescent biosensor as described herein; and detecting luminescence of the treated cell; wherein an intensity of the luminescence is indicative of amount of activity of the Hippo signaling pathway. In one embodiment, an intensity of the luminescence is indicative of amount of LATS kinase activity in the Hippo signaling pathway. In one embodiment, an intensity of the luminescence is indicative of amount of YAP-TEAD interaction in the Hippo signaling pathway. In one embodiment, treating a cell comprises transfecting a cell with the luminescent biosensor. In one embodiment, treating a cell comprises lysing the cell and combining a cell lysate with the luminescent biosensor.

In one embodiment, the method comprises: non-invasively monitoring and/or quantifying in real-time, in vitro or in vivo, activity of LATS kinase, comprising transfecting the cell with a luminescent biosensor as described herein, and detecting luminescence; wherein an intensity of the luminescence is indicative of amount of LATS kinase activity in the Hippo signaling pathway.

In one embodiment, the method comprises: non-invasively monitoring and/or quantifying in real-time, in vitro or in vivo, YAP-TEAD interaction, comprising transfecting the cell with a luminescent biosensor as described herein, and detecting luminescence; wherein an intensity of the luminescence is indicative of amount of YAP-TEAD interaction in the Hippo signaling pathway.

Another aspect of the invention relates to a method, comprising: monitoring and/or quantifying activity of one or more proteins of the Hippo signaling pathway, comprising combining the one or more proteins with a luminescent biosensor as described herein and at least one substance, and detecting luminescence of the luminescent biosensor; wherein an intensity of the luminescence is indicative of effect of the at least one substance on activity of the one or more proteins of the Hippo signaling pathway.

In various embodiments of the above method, the at least one substance is selected from a chemical compound such as a small molecule inhibitor (e.g., molecular weight below about 500 Daltons), a large molecule inhibitor (e.g., molecular weight above about 500 Daltons), a biological agent (e.g., antibody), protein, polypeptide, peptide, DNA aptamer, microRNA, interfering RNA (shRNA, siRNA), a sugar, lipid, glycoprotein, and glycolipid.

Another aspect of the invention relates to a method for monitoring and/or quantifying activity of the Hippo signaling pathway in a biological sample obtained from a subject, comprising: treating cells of the biological sample with at least one reagent comprising the a luminescent biosensor as described herein; and detecting luminescence of the treated biological sample; wherein an intensity of the luminescence is indicative of amount of activity of the Hippo signaling pathway. In one embodiment, an intensity of the luminescence is indicative of amount of LATS kinase activity in the Hippo signaling pathway. In one embodiment, an intensity of the luminescence is indicative of amount of YAP-TEAD interaction in the Hippo signaling pathway. In various embodiments, the biological sample comprises at least one of tissue and blood. In one embodiment, the biological sample comprises blood. In one embodiment, an intensity of the luminescence is indicative of the cells being cancer cells.

Another aspect of the invention relates to a kit, comprising: a luminescent biosensor as described herein; at least one reagent; and, optionally, instructions for using the kit.

BRIEF DESCRIPTION OF THE DRAWINGS

For a greater understanding of the invention, and to show more clearly how it may be carried into effect, embodiments will be described, by way of example, with reference to the accompanying drawings, wherein:

FIG. **1**A is a schematic diagram of YAP1 protein structure (SEQ ID NO:2) showing LATS phosphorylation site (S127) and the surrounding 15 amino acid sequence (YAP15; SEQ ID NO:7).

FIG. **1**B is a western blot for GST pulldown assays showing results confirming that YAP15 is sufficient for interaction with cytoplasmic protein 14-3-3 in vitro.

FIG. **2**A shows schematic diagrams of domain structures of a LATS intermolecular biosensor, referred to as Nluc-YAP15 (upper; SEQ ID NOs:6, 7) and 14-3-3-Cluc (lower; SEQ ID NOs:4, 6), according to an embodiment of the invention.

FIG. **2**B is a schematic diagram showing the mechanism by which a LATS intermolecular biosensor determines LATS kinase activity.

FIG. **2**C shows experimental results validating LATS intermolecular biosensor activity, where biosensor activity or NLuc-YAP15-S127 phosphorylation status were determined in HEK293 cells 48 hours after transfection by luciferase assay or western blot, respectively. Data are presented as mean±SD, n=3.

FIG. **2**D shows experimental results confirming that a LATS intermolecular biosensor responds specifically to LATS kinase activity, by mutation of the LATS kinase consensus motif (HXRXXS/T; H, histidine; R, arginine; X, any amino acid; S, serine; T, threonine; SEQ ID NOs:71, 72) in Nluc-YAP15 (SEQ ID NOs:7, 8). Data are presented as mean±SD, n=3.

FIG. **2**E shows experimental results confirming that LATS intermolecular biosensor activity is reduced by MST or LATS knockout. Data are presented as mean±SD, n=3.

FIG. **2**F shows experimental results confirming that LATS intermolecular biosensor can be stably expressed to detect LATS kinase activity, wherein biosensor activity and phosphorylation status were monitored in a HEK293A cell line with doxycycline (Dox)-inducible LATS2 overexpression and stable LATS biosensor (LATS-BS) expression, and biosensor activity and phosphorylation status of endogenous YAP (YAP-pS127) and Nluc-YA15P-S127 (Nluc-YAP15-

pS127) were determined at the indicated times by luciferase assay and western blot, respectively. Data are presented as mean±SD, n=3.

FIG. **3**A is a schematic diagram showing the domain structure of a LATS intramolecular biosensor based on SEQ ID NOs:6, 7, 73, according to one embodiment.

FIG. **3**B is a schematic diagram showing the mechanism by which a LATS intramolecular biosensor determines LATS kinase activity.

FIG. **3**C is a bar chart showing results of a validation study of an intramolecular LATS biosensor according to the embodiment of FIG. **3**A.

FIG. **4**A is a schematic diagram showing the domain structure of an engineered LATS biosensor based on SEQ ID NOs:6, 7, according to one embodiment.

FIG. **4**B is a schematic diagram showing the mechanism by which an engineered LATS biosensor determines LATS kinase activity.

FIG. **4**C is a bar chart showing results of a validation study of an engineered LATS biosensor according to the embodiment of FIG. **4**A.

FIGS. **5**A-**5**D show diagrams of multiple cloning sites of vectors (pBiT1.1-N [TK/LgBiT; 5A]; pBiT2.1-C [TK/SmBiT; 5B]; pET16b (5C)) and domain structures of constructs (5D) used to make NanoBiT (NanoLuc) biosensors based on Nluc and CLuc (SEQ ID NO:6), YAP15 (SEQ ID NO:7), LgBiT (SEQ ID NO:52), SmBiT (SEQ ID NO:54), and 14-3-3 (SEQ ID NO:4), according to embodiments of the invention.

FIG. **6** is a schematic diagram showing an overview of a NanoBiT interaction system of a LATS NanoBiT biosensor according to an embodiment of the invention.

FIG. **7** shows a coomassie brilliant blue (CBB) stained SDS-PAGE of purified proteins for a LATS NanoBiT biosensor.

FIG. **8**A shows results of a NanoBiT biosensor assay of overexpressed LgBiT-YAP15 WT and mutant (MUT) and 14-3-3-SmBiT in HEK293T cells as relative luminescence to YAP15MUT-14-3-3.

FIG. **8**B shows results of a NanoBiT LATS biosensor assay for cancer cells.

FIG. **8**C shows results of a NanoBiT LATS biosensor assay for blood.

FIG. **9** shows results of an in vitro NanoBiT biosensor assay using purified LgBiT-YAP15 (WT and mutant), 14-3-3-SmBiT, and LATS2 kinase; upper panel shows the result of the NanoBiT assay for YAP15WT or mutant at two different concentrations of biosensor (5 and 100 ng) as a ratio of luminescence signal at different time points; lower panel shows immunoblotting analysis and ponceau staining of the respective samples with 100 ng of biosensor.

FIG. **10** shows the results of a kinase assay with purified proteins; upper panel shows the NanoBiT LATS biosensor assay for YAP15 WT and mutant (100 ng) with and without lambda phosphatase after 30 min; the lower panels show the relative immunoblotting and Ponceau staining for the respective samples.

FIG. **11** shows diagrams of domain structures of eight constructs used to make a YAP-TEAD biosensor based on LgBiT (SEQ ID NO:52), SmBiT (SEQ ID NO:54), YAP50-171 (SEQ ID NO:2), and TEAD1-194-411 (SEQ ID NO:50), according to one embodiment.

FIG. **12** shows a schematic overview of a NanoBiT interaction system of a YAP-TEAD NanoBiT biosensor according to an embodiment of the invention.

FIG. **13** shows the results of an assay of overexpressed YAP50-171 of SEQ ID NO:2 and TEAD1-194-411 of SEQ ID NO:50 in HEK293T cells lysed with passive lysis buffer, for a biosensor with a combination of SmBiT-YAP50-171 (SEQ ID NO:2) and LgBiT-TEAD1-194-411 of SEQ ID NO:50 constructs.

FIG. **14** shows the results of an assay for analyzing LATS kinase activity under various stimuli regulating Hippo signaling by live cell luciferase imaging, using an intermolecular LATS-BS as described herein.

FIG. **15** is a photomicrograph showing the results of an experiment to determine subcellular LATS kinase activity using an intermolecular LATS-BS as described herein, obtained by bioluminescent microscopy.

FIG. **16** is a photograph showing LATS kinase activity in mice by in vivo luciferase imaging, using an intermolecular LATS-BS as described herein.

FIG. **17**A is a schematic diagram showing a method for a screening assay, and FIG. **17**B shows the results of a screening assay for identifying novel regulators of LATS using an intermolecular LATS-BS as described herein and a kinase inhibitor screen.

DETAILED DESCRIPTION OF EMBODIMENTS

In practicing the embodiments described herein, many conventional techniques in cell biology, molecular biology, protein biochemistry, immunology, and bacteriology are used. These techniques are well-known in the art and are provided in any number of available publications, such as Current Protocols in Molecular Biology, Vols. I-III, Ausubel, Ed. (1997); Sambrook et al., Molecular Cloning: A Laboratory Manual, Second Ed. (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989). Unless specifically defined herein, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

One aspect of the invention relates to bioluminescence-based biosensor constructs that non-invasively monitor real-time in vitro and in vive activity of LATS kinase, the central player of the Hippo signaling pathway. A LATS biosensor (LATS-BS) as described herein quantifies LATS kinase activity by split luciferase assay, a bioluminescence-based technique that non-invasively monitors protein-protein interactions in vitro and in vive in real-time with accurate quantification, high sensitivity, and excellent reproducibility. Embodiments of the biosensor constructs include fragments of firefly (*Photinus* sp., e.g., *Photinus pyralis*) or NanoBiT (also referred to as NanoLuc) luciferase and human YAP1. Some embodiments include human cytoplasmic protein 14-3-3 or a fragment thereof.

Another aspect of the invention relates to a method for non-invasively monitoring real-time in vitro and in vivo activity of LATS kinase. In various embodiments, the method includes using a LATS biosensor as described herein to quantify LATS kinase activity. The embodiments provide a bioluminescence-based technique for monitoring LATS kinase activity with accurate quantification, high sensitivity, and excellent reproducibility (see Examples for details).

A third aspect of the invention relates to bioluminescent biosensor constructs and methods for non-invasively monitoring YAP-TEAD interaction, a critical step in regulation of downstream target by the Hippo pathway. Embodiments of the biosensor constructs include fragments of NanoBiT luciferase and fragments of human YAP1 and TEAD1, or functional equivalents thereof, and provide a bioluminescent-based technique for monitoring YAP and TEAD interactions both in vitro and in vivo with high sensitivity, stability, and reproducibility.

At least eight isoforms of YAP1 are known. SEQ ID NO:1 shows the full human YAP2L isoform mRNA (accession number: AB567720) and SEQ ID NO:2 shows the amino acid sequence. The fragments used in the embodiments described herein were obtained from the YAP2L isoform of YAP1 (SEQ ID NO:2). However, the fragments used in the embodiments described herein may be obtained from any of the isoforms, or may be functional equivalents thereof. In this disclosure, the terms "YAP1" and "YAP" are used interchangeably to refer to an isoform of YAP1. SEQ ID NO:3 shows the full human 14-3-3 protein theta mRNA (accession number: P27348) and SEQ ID NO:4 shows the amino acid sequence. SEQ ID NO:5 shows the full length firefly luciferase mRNA and SEQ ID NO:6 shows the luciferase protein.

Since LATS phosphorylates S127 on YAP1 and cytoplasmic protein 14-3-3 binds specifically to phosphorylated but not un-phosphorylated S127-YAP, embodiments were constructed for monitoring LATS kinase activity by measuring the pS127-YAP/14-3-3 interaction.

In various embodiments, a LATS-BS includes a minimal YAP1 fragment that interacts with 14-3-3 in a phosphorylation-dependent manner. The full length YAP1 protein was not used to avoid confounding signals by post-translational modifications of YAP1 by other upstream regulators. In one embodiment, the minimal YAP1 fragment includes 15 amino acids (YAP15) surrounding the 5127 LATS phosphorylation site (amino acids 120-134; SEQ ID NO:7; FIG. **1**A). Functional equivalents may be used, such as other sizes of YAP1 fragments, such as, for example, longer (e.g., 16-20 amino acids) or shorter (e.g., 12-14 amino acids) surrounding the S127 (SEQ ID NO:2). Embodiments may include a YAP fragment with a HxRxxS motif (SEQ ID NO:71). Since H, R, and S residues but not other amino acids in the HxRxxS motif (SEQ ID NO:71) on the YAP fragment are essential for LATS biosensor function (see, e.g., FIG. **2**D), variants of YAP fragments with changes of amino acids other than H/R/S may also be used. Larger fragments (e.g., 20-100 amino acids) may result in confounding signals.

Minimal YAP1 fragments were tested for interaction with 14-3-3 after phosphorylation by LATS2 kinase. Using in vitro GST-pulldown assays, it was found that like full-length YAP-GST, YAP15-GST could directly bind to 14-3-3 after LATS phosphorylation while a phosphorylation-mutant YAP15-S127A-GST (A, alanine) could not. FIG. **1**B shows that YAP15 is sufficient for interaction with 14-3-3 in vitro. To collect the data, GST-tagged full length YAP (YAP-GST), YAP15 with wild type sequence (YAP15-S127-GST), or mutant YAP15 that cannot be phosphorylated by LATS (YAP15-S127A-GST) was purified from bacterial cells and 1 μg of GST fusion protein was incubated for 20 minutes at 30° C. with recombinant LATS kinase. 100 μg of cell lysate from human embryonic kidney cells (HEK293) transiently expressing 14-3-3-Flag was added and YAP or YAP15-S127 or YAP15-S127A/14-3-3 binding was assessed by GST pull-down with protein S-agarose beads, followed by western blot with anti-Flag (14-3-3-Flag) and anti-YAP-pS127 antibodies. The membrane was stained with Ponceau S to visualize the fusion proteins.

Since the TEAD family consists of four members, other TEADs (TEAD2-4) may also be used to replace TEAD1 to make biosensors similar to the YAP-TEAD1 biosensor. Throughout this disclosure, "TEAD1" and "TEAD" are used interchangeably to refer to any one of the TEAD family members.

In the following descriptions of various embodiments of the biosensor, references to sequences and sequence listings are made. Those of ordinary skill in the art will readily appreciate that the invention is not limited to the specific sequences described, as many variants are possible without departing from the invention. For example, substitutions, mutations, deletions, and/or additions of one or more nucleotides or amino acids may be made, or may occur, without substantial effect on functional properties of a biosensor. Such a functional equivalent may have, for example, 60%, or 70%, or 80%, or 90%, or more sequence identity with a sequence described herein. Such functional equivalents are intended to be included in the embodiments of the invention.

1. LATS Biosensor

1.1 Intermolecular Biosensor

The biosensor was made by overlapping PCR using firefly luciferase as a template. YAP15 and 14-3-3 were fused with N-terminal and C-terminal luciferase fragments (Nluc and Cluc), respectively, to create a LATS-B S. As shown in FIG. **2**A, for Nluc-YAP15, firefly luciferase amino acids 1-416 (N-luciferase, Nluc) (SEQ ID NO: 6) were fused to the N-terminal of YAP15 (120-134; SEQ ID NO:7) separated by a glycine/alanine linker (GGAGG; SEQ ID NO:73); and for 14-3-3-Clue, luciferase amino acids 394-550 (C-luciferase, Cluc; SEQ ID NO:6) were fused to the C-terminal of 14-3-3 (SEQ ID NO: 4) separated by a glycine/serine linker (GGSGGGGSGG; SEQ ID NO:74). Biosensors were cloned into the BamHI/NotI sites of the pcDNA3.1/hygro (+) vector (SEQ ID NO:9, purchased from Invitrogen, Dublin, Ireland). Primers are shown in SEQ ID NOs:10-16. The full length sequences for Nluc-YAP15 and 14-3-3-Clue in pcDNA3.1/hygro (+) vector are given in SEQ ID NOs:57 and 58, respectively, wherein the underlined portions are the main constructs and the rest is the vector.

The mechanism of action for how the LATS-BS determines LATS kinase activity is shown in FIG. **2**B. At baseline, there is no interaction between YAP15 and 14-3-3 so the LATS-BS shows minimal bioluminescence activity. However, LATS-dependent phosphorylation of YAP15-S127 leads to 14-3-3 binding, luciferase complementation, and high bioluminescence signal.

In a validation study, LATS-BS was transfected alone or together with LATS2 or/and MST2 into HEK293 cells and biosensor activity or NLuc-YAP15-S127 phosphorylation status were determined 48 hours after transfection by luciferase assay or western blot, respectively. As depicted in FIG. **2**C, HEK293 cells transfected with LATS-BS alone had low luciferase activity and this was correlated with a low degree of Nluc-YAP15-S127 phosphorylation. Co-transfection of LATS-BS with MST2 was associated with increases in both Nluc-YAP-S127 phosphorylation and luciferase activity, and this effect was suppressed with lysophosphatidic acid (LPA), an inhibitor of the Hippo pathway. For lysophosphatidic acid (LPA) treatment, cells were stimulated with 10 μM LPA for 1 hour before collection (n=3). LATS-BS co-expression with both MST2 and LATS2 was correlated with further increases in Nluc-YAP15-S127 phosphorylation and luciferase activity. Collectively, these observations are consistent with a model where MST2 activates

LATS2, which phosphorylates Nluc-YAP15-S127, leading to binding with Cluc-14-3-3 and reconstitution of active luciferase.

To further validate the biosensor construct model, conserved residues (H, histidine; R, arginine; S) within the LATS consensus phosphorylation motif (HxRxxS/T; x, any amino acid; SEQ ID NOs: 71, 72) on Nluc-YAP15-S127 were mutated to A (H122A, R124A, and S127A). Each individual mutation completely abolished Nluc-YAP15-S127 phosphorylation and LATS-BS luciferase activity, as shown in FIG. **2**D. In addition, the basal LATS-BS signal was reduced by knockout of endogenous MST1/2 in HEK293A (50% reduction) or more dramatically by LATS1/2 knockout HO % reduction), as shown in FIG. **2**E. LATS-BS was transfected into CRISPR-Cas9-generated LATS1/2 or MST1/2 knockout HEK293A and basal biosensor activity was determined 48 hours after transfection (n=3). Furthermore, inducible expression of LATS2 in HEK293A cells stably expressing LATS-BS showed that the levels of LATS2 are correlated with the level of endogenous YAP-pS127, Nluc-YAP15-pS127 as well as with LATS-BS activity, as shown in FIG. **2**F. Biosensor activity and phosphorylation status were monitored in a HEK293A cell line with doxycycline (Dox)-inducible LATS2 overexpression and stable LATS-BS expression. Cells were treated with 1 μg/mL Dox for the indicated times and biosensor activity and phosphorylation status of endogenous YAP (YAP-pS127) and Nluc-YA15P-S127 (Nluc-YAP15-pS127) were determined by luciferase assay and western blot, respectively (n=3).

This LATS biosensor was also used to examine LATS kinase activity in living cells and mice and to perform a screening assay for regulators of LATS (see details in Examples).

1.2 Intramolecular Biosensor

An intramolecular biosensor was made by overlapping PCR using firefly luciferase as a template. In one embodiment, firefly luciferase amino acids 1-416 (N-luciferase, Nluc; SEQ ID NO:6) were fused to the N-terminal of YAP15 (120-134) (SEQ ID NO:7) separated by a glycine/alanine linker (GGAGG; SEQ ID NO:73). Within the same open reading frame, luciferase amino acids 394-550 (C-luciferase, Cluc; SEQ ID NO:6) were fused to the C-terminal of 14-3-3 separated by a glycine/alanine linker. For this biosensor, LATS phosphorylates YAP15-5127 to cause a conformational change in the intramolecular LATS-BS, leading to luciferase complementation and detectable biosensor activity. Primers are shown in SEQ ID NOs:10, 16, 17, and 18.

The domain structure is shown in FIG. **3**A and the mechanism of action for how the LATS-BS determines LATS kinase activity is shown in FIG. **3**B. At baseline, there is no interaction between YAP15 and 14-3-3 so the LATS-BS shows minimal bioluminescence activity. However, LATS-dependent phosphorylation of YAP15-S127 leads to 14-3-3 binding, luciferase complementation, and high bioluminescence signal.

To validate the intramolecular biosensor, the biosensor was transfected alone or together with LATS2 or/and MST2 into HEK293 cells and biosensor activity was determined 48 hours after transfection by luciferase assay. For LPA treatment, cells were stimulated with 10 μM LPA, an inhibitor of the Hippo pathway, for 1 hour before collection (n=3). Results are shown in FIG. **3**C.

13 Engineered Biosensor

The biosensor was made by overlapping PCR using firefly luciferase as a template. In one embodiment, the C-terminal seven amino acids from firefly luciferase were removed to create Eng-luc (544 amino acids). This construct was fused to the N-terminal of YAP15 (amino acids 120-134; SEQ ID NO:7). This brings the luciferase site in close proximity to YAP15-5127 such that LATS-dependent phosphorylation of YAP-S127 modulates luciferase activity directly. Primers are shown in SEQ ID NOs:10 and 19.

The domain structure of the Eng-luc LATS biosensor according to one embodiment is shown in FIG. **4**A and the mechanism of action for how the biosensor determines LATS kinase activity is shown in FIG. **4**B.

For validation of the Eng-luc LATS-BS, the biosensor was transfected alone or together with LATS2 or/and MST2 into HEK293 cells and biosensor activity was determined 48 hours after transfection by luciferase assay. For LPA treatment, cells were stimulated with 10 μM LPA for 1 hour before collection (n=3). Results are shown in FIG. **4**C.

1.4. NanoBiT Biosensor

For this biosensor YAP15 (aa 120-134; SEQ ID NO:7) and 14-3-3 full length (aa 1-245; SEQ ID NO:4) were used. As shown in FIG. **7**-**10**, a YAP15 mutant was used as a negative control in these experiments.

To clone YAP15 and 14-3-3 in NanoBiT (also referred to as NanoLuc) vectors (purchased from Promega Corporation, Madison, Wis., U.S.A.), primers with EcoR1 and Bglll restriction sites were used. For the LgBiT-YAP15 construct, primers shown in SEQ ID NOs:20-23 were used. For the 14-3-3-SmBiT construct, primers shown in SEQ ID NOs: 24-25 were used.

In the case of YAP15WT (S127; SEQ ID NO:7) and mutant (A127; SEQ ID NO:8), primers with EcoR1 and Bglll flanking ends were annealed first and then they were ligated into digested pBiT 1.1 N (TK-LgBiT) vector (SEQ ID NO:26; purchased from Promega Corporation) with N-terminal LgBiT domain. FIG. **5**A shows the multiple cloning site. For making the 14-3-3-SmBiT construct, in order to amplify 14-3-3 gene, standard PCR using the above mentioned primers was done by using 14-3-3 as a template. PCR product was digested using EcoR1 and Bglll restriction enzymes and was ligated into pBiT 2.1 C (TK-SmBiT; purchased from Promega Corporation) (SEQ ID NO:27) with SmBiT (11 amino acid) sequence at the C-terminus. FIG. **5**B shows the multiple cloning site.

To make LgBiT-YAP15 (WT and mutant) and 14-3-3-SmBiT constructs for protein expression and purification in *E. coli*, the primers shown in SEQ ID NOs:28-30 were used for the LgBiT-YAP15 construct, and the primers shown in SEQ ID NOs:31-32 were used for the 14-3-3-SmBiT construct. For PCR, LgBiT-YAP15 and 14-3-3-SmBiT in NanoBiT vectors were used as template. pET16b vector (SEQ ID NO:33; purchased from Novagen (Millipore (Canada) Ltd., Etobicoke, Canada) was used for overexpression of LgBiT-YAP15 (WT and mutant) and 14-3-3-SmBiT as His-tagged proteins. FIG. **5**C shows the multiple cloning site.

FIG. **5**D shows a schematic representation of the LgBiT-YAP15 and 14-3-3-SmBiT constructs. SEQ ID NOs:59, 60, 61, and 62 give the full length sequences for LgBiT-YAP15 in pBiT 1.1 N vector, 14-3-3-LgBiT in pBiT2.1-C vector, LgBiT-YAP15 in pET16b vector, and SmBiT in pET16b vector, respectively, wherein the underlined portions are the main constructs and the rest is the vector.

FIG. **6** is a schematic diagram showing an overview of the NanoBiT interaction system. YAP15 and 14-3-3 are fused to LgBiT and SmBiT, respectively. Interaction of purified fusion proteins or overexpressed proteins in the cells leads to structural complementation of LgBiT with SmBiT that consequently generates a functional enzyme with bright luminescence.

For protein expression, the *E. coli* strain CodonPlus (DE3)-RIPL was transformed and used to purify the respective proteins. *E. coli* with the respective construct were grown until an OD600 value of 0.6-0.8 and then induced with 0.3 mM isopropyl-β-D-thiogalactopyranoside (IPTG) overnight at 20° C. Protein purification was carried out by incubating cells at 4° C. with DNase I (10 μg/ml) followed by cell lysis by sonication. Bacterial lysates were centrifuged to collect soluble fractions and His-tagged proteins were purified from the supernatant via Ni-affinity purification. After eluting and concentrating, proteins were subjected to dialysis against standard buffer containing 30 mM Tris-HCl, pH 7.5, 150 mM NaCl, 5 mM MgCl2, and 2 mM DTT. All purified proteins were analyzed by SDS-PAGE and stored at −80° C. FIG. **7** shows coomassie brilliant blue (CBB) stained SDS-PAGE of purified proteins for the biosensor.

NanoBiT Assay for YAP15-14-3-3 in Cells.

A NanoBiT assay was prepared for YAP15-14-3-3 in cells. HEK293T cells (3×10^5) were transfected using Polyjet transfection reagent according to the manufacturer's instructions in 12-well plates by using 250 ng of each plasmid DNA per transfection. After 48 h the cells were lysed with passive lysis buffer and the NanoBiT assay of overexpressed LgBiT-YAP15 WT and mutant and 14-3-3-SmBiT was performed. Relative luminescence to YAP15MUT-14-3-3 was determined as shown in FIG. **8**A.

NanoBiT Assay for YAP15-14-3-3 Using Cancer Cells.

Cancer cells (A549, H1299, and HEK293) were treated with okadaic acid for 1 h to activate LATS before lysing with passive lysis buffer. Then, 350 μg cell lysate was untreated or treated with calf intestine phosphatase (CIP) to inactivate the biosensor, followed by LATS pulldown and measurement of LATS kinase activity in vitro using purified LATS BS. As shown in FIG. **8**B, the NanoBiT LATS-BS produced a strong signal for all three types of cancer cells.

NanoBiT Assay for YAP15-14-3-3 Using Blood.

Mononuclear cells were separated from fresh human blood and then lysed with passive lysis buffer. Then, 350 μg cell lysate was used to pull-down LATS kinase and measure its activity in vitro using purified NanoBiT LATS-BS. As shown in FIG. **8**C, the NanoBiT LATS-BS produced a strong signal.

NanoBiT Assay Using Purified Proteins.

In order to test the LATS NanoBiT biosensor in vitro, a kinase assay was done using purified LgBiT-YAP15 (WT and mutant), 14-3-3-SmBiT and LATS2 as the kinase. The assay was done with two different concentrations of biosensor (100 ng and 5 ng). After 1, 10, 20, 30 min and 1, 2, 4 and 20 h luminescence was measured and also phosphorylation level was checked using WB. Results are shown in FIG. **9**. The upper panel shows the result of NanoBiT assay for YAP15WT and mutant at the two different concentrations of biosensor (5 and 100 ng) as a ratio of luminescence signal in the presence to absence of LATS as a kinase in different time points. The lower panel shows immunoblotting analysis and Ponceau staining of the respective samples from the experiment with 100 ng of biosensor.

Kinase Assay with and without Phosphatase.

To confirm that the biosensor is phosphorylation dependent and works through LATS, lambda phosphatase was used and luminescence as well as phosphorylation was determined. The results show that treating with lambda phosphatase abolishes luminescence. In FIG. **10** the upper panel shows the result of an assay for the biosensor with YAP15 WT or mutant (100 ng) with and without lambda phosphatase after 30 min. The Y axis shows the ratio of luminescence in the presence of LATS and in the absence of LATS. The lower panels show the relative immunoblotting and Ponceau staining for the respective samples

2. YAP-TEAD Biosensor

YAP transcriptionally activates downstream genes by interacting with the TEAD family of transcription factors (i.e., TEAD1-4). To monitor interaction between YAP and TEAD, a NanoBiT split luciferase biosensor was developed that quantifies YAP1 and TEAD1 interaction. This biosensor is based on a YAP fragment (residues 50-171; SEQ ID NO:2)-TEAD1 fragment (residues 194-411; SEQ ID NO:50) complex, in which YAP wraps around the globular structure of TEAD1. FIG. **12** shows a schematic overview of the NanoBiT interaction system of a YAP-TEAD NanoBiT biosensor as described herein. The YAP1 mRNA and amino acid sequences are given in SEQ ID NOs:1 and 2, respectively. The TEAD1 mRNA and protein sequences are given in SEQ ID NOs:49 and 50, respectively. The Large BiT (LgBiT) mRNA and protein sequences are given in SEQ ID NOs:51 and 52, respectively. The Small BiT (SmBiT) mRNA and protein sequences are given in SEQ ID NOs:53 and 54, respectively. The vectors were pcDNA3.1/hygro(+) (SEQ ID NO:9), pcDNA3.1/hygro(+)-Flag (SEQ ID NO:55), and pcDNA3.1/hygro(+)-Myc (SEQ ID NO:56).

Eight NanoBit split luciferase constructs were made using the primers as listed below. The domain structures of the eight constructs are shown in FIG. **11**.

Construct 1:

LgBiT-YAP50-171-Flag (overlapping PCR):

SEQ ID NO:34. B1-Kozak-LgBiT-F primer (41 nucleotides):

SEQ ID NO:35. LgBiT-(GS)-R primer (54 nucleotides):

SEQ ID NO:36. (GS)-YAP50-F primer (69 nucleotides):

SEQ ID NO:37. N1-YAP171-Flag-R primer (63 nucleotides)

Construct 2:

Flag-YAP50-171-LgBiT (overlapping PCR):

SEQ ID NO:38. B1-YAP50-F primer (32 nucleotides):

SEQ ID NO:39. (GS)-YAP171-R primer (68 nucleotides):

SEQ ID NO:40. (GS)-LgBiT-F primer (66 nucleotides):

SEQ ID NO:41. N1-LgBiT-R primer (43 nucleotides):

Construct 3:

SmBiT-YAP50-171-Flag (tandem PCR):

SEQ ID NO:42. B1-Kozak-SmiBiT-(GS)-F primer (98 nucleotides):

SEQ ID NO:36. (GS)-YAP50-F primer (69 nucleotides):

SEQ ID NO:37. N1-YAP171-Flag-R primer (63 nucleotides)

Construct 4:

Flag-YAP50-171-SmBiT (tandem PCR):

SEQ ID NO:38. B1-YAP50-F primer (32 nucleotides)

SEQ ID NO:39. (GS)-YAP171-R primer (68 nucleotides)

SEQ ID NO:43. N1-SmBiT-(GS)-R primer (97 nucleotides):

Construct 5:

LgBiT-TEAD1-194-411-Myc (overlapping PCR):

SEQ ID NO:34. B1-Kozak-LgBiT-F primer (41 nucleotides)

SEQ ID NO:35. LgBiT-(GS)-R primer (54 nucleotides)

SEQ ID NO:44. (GS)-TEAD-194-F primer (73 nucleotides):

SEQ ID NO:45. N1-TEAD411-Myc-R primer (73 nucleotides):

Construct 6:

Myc-TEAD1-194-411-LgBiT (overlapping PCR)

SEQ ID NO:46. B1-TEAD194-F primer (36 nucleotides):

SEQ ID NO:47. GS-TEAD-411-R primer (69 nucleotides):

SEQ ID NO:40. (GS)-LgBiT-F primer (66 nucleotides)

SEQ ID NO:41. N1-LgBiT-R primer (43 nucleotides)

Construct 7:

SmBiT-TEAD1-194-411-Myc (tandem PCR)

SEQ ID NO:42. B1-Kozak-SmiBiT-(GS)-F primer (98 nucleotides)

SEQ ID NO:48. (GS)-TEAD194-F primer (73 nucleotides):

SEQ ID NO:45. N1-TEAD411-Myc-R primer (73 nucleotides)

Construct 8: Myc-TEAD-194-411-SmBiT (tandem PCR)

SEQ ID NO:46. B1-TEAD194-F primer (36 nucleotides)

SEQ ID NO:47. GS-TEAD-411-R primer (69 nucleotides)

SEQ ID NO:43. N1-SmBiT-(GS)-R primer (97 nucleotides)

Cloning.

To make constructs 1 and 5, overlapping PCR was performed using the above primers, and they were inserted into BamH1/Not1 cloning site of pcDNA3.1/hygro. For construct 1, pBiT1.1-N(TK/LgBiT) and full length YAP were used as templates to perform PCR. For construct 5, pBiT1.1-N(TK/LgBiT) and full length TEAD1 were used to perform PCR.

To make constructs 2 and 6, overlapping PCR was performed using the above primers, and they were inserted into BamH1/Not1 cloning site of pcDNA3.1/hygro-Flag/Myc. For construct 2, pBiT1.1-C(TK/LgBiT) and full length YAP were used to perform PCR. For construct 6, pBiT1.1-C(TK/LgBiT) and full length TEAD1 were used to perform PCR.

To make constructs 3 and 7, tandem PCR was performed using the above primers, and they were inserted into BamH1/Not1 cloning site of pcDNA3.1/hygro. For both constructs full length YAP and TEAD1 were used respectively to perform PCR.

To make construct 4 and 8, overlapping PCR was performed using the above primers, and they were inserted into BamH1/Not1 cloning site of pcDNA3.1/hygro-Flag/Myc. For both constructs full length YAP and TEAD1 were used respectively to perform PCR.

SEQ ID NOs:63-70 give the full length sequences for constructs 1-8, respectively, wherein, in each sequence, the underlined portion is the main construct and the rest is the vector.

Validation.

Different combinations of the eight constructs were used in assays in order to find the best orientation for the biosensor. The assays used overexpressed YAP50-171 and TEAD1-194-411 in HEK293T cells lysed with passive lysis buffer. All combinations of SmBiT and LgBiT biosensors worked, but the combination of SmBiT-YAP50-171 and LgBiT-TEAD1-194-411 showed the highest signal and sensitivity (FIG. **13**).

Discussion

The embodiments and experiments described herein establish the LATS biosensor embodiments as the first LATS biosensor that can accurately monitor LATS kinase activity and intensity of Hippo signaling in vitro and in vivo, and its use in a new bioluminescence (BLI) method. In addition, the embodiments and experiments described herein establish the YAP-TEAD biosensor embodiments as the first biosensor that can accurately monitor YAP and TEAD interaction, which is essential for elucidating the function of YAP in the Hippo pathway. Although BLI is widely used for reporting promoter activity and imaging tumors in mice, few studies have used it to measure protein function at the cellular level and even fewer studies have examined subcellular protein function using bioluminescence microscopy. The ability to detect LATS kinase activity in individual cells and in blood as provided by the embodiments described herein has applications for evaluating heterogeneous dynamics of LATS kinase activity in cell culture as well as for the real-time monitoring of Hippo signaling responses to various drug treatments, and in applications such as detecting Hippo pathway signaling in biological samples such as tissue and blood obtained from subjects. In particular, the results show that a biosensor as described herein may be useful for detecting cancerous cells in biological samples such as tissue. The results of in vivo experiments in mice further illustrate how LATS-BS embodiments may be used to preclinically examine the effects of a variety of drugs on LATS kinase activity in vivo.

A biosensor as described herein may be provided in a kit to measure the Hippo signaling pathway, for use in vitro and in vivo. For example, a kit may include one or more LATS biosensor such as an intermolecular biosensor, intramolecular biosensor, engineered biosensor, or NanoBiT biosensor, and/or a YAP-TEAD biosensor as described herein, optionally with one or more reagents suitable for using the kit in an assay for a specified biological sample or cell type, and instructions for proper use of the kit. The reagent may be, for example, a reagent appropriate for in vitro use or for in vivo use, a buffer, cell lysis buffer, etc.

Example

The following example provides details of the methods used to make and use an intermolecular LATS biosensor as described herein.

1. Determine activity of purified LATS protein and LATS in cells by in vitro luciferase assay (described above and shown in FIGS. **2**C, **2**D, **3**C, **8**, and **13**).

2. Determine interaction of YAP and TEAD in cells by in vitro luciferase assay (described above and shown in FIG. **13**).

3. Determine LATS kinase activity under various stimuli regulating Hippo signaling by live cell luciferase imaging.

For live cell imaging, LATS-BS or a pGL3-control vector were transfected into HEK293, MDA-MB-231 or A549 cells. After 48 hours, cells were trypsinized and collected in a black, clear bottomed, 96-well plate. 150 μg/mL D-luciferin (D-Luciferin, Potassium Salt, GoldBio #LUCK-250) in media was added to each well 5-10 min before imaging. Exposure time for images was approximately 3 min/plate. Imaging was performed using a LightTools Research system

(Synopsys, Ltd., Mountain View, Calif., USA) dark box and a Hamamatsu ORCA-Flash4.0 V2 digital CMOS camera over the course of 20 minutes to establish optimal peak luciferase activity. The bioluminescence of the regions of interest was analyzed for total emission flux using Image-Pro® Plus software (Media Cybernetics, Inc., Rockville, Md., USA).

Experiments were conducted to further validate the LATS intermolecular biosensor and explore potential applications for its use. The LATS-BS responded to numerous signals reported to modulate Hippo pathway activity, including cell confluency, drugs activating Hippo signaling (Forskolin, PI3K inhibitor, PDK inhibitor, F-IBMX, and 2-deoxy-glucose) and Hippo signaling inhibitors (LPA, EGF, Insulin, S1P, and TPA). The LATS-BS is activated by LATS in various cell lines (e.g., A549, MDA-MB231). Notably, in these experiments biosensor activity was measured in both cell lysates and in live cells using luciferase assay and BLI respectively. Collectively, these data illustrate the broad range of potential applications for the LATS-BS in monitoring Hippo pathway activity.

The following compound treatments were used for in vitro luciferase assay and live cells imaging: RAF inhibitor (GW5054, Cayman Chemical, Ann Arbor, Mich., USA), ATR inhibitor (CGK733, Cayman Chemical), PI3K inhibitor 1 (GDC0941, Cayman Chemical), PI3K inhibitor 2 (LY294002, Cayman Chemical), PDK inhibitor (GSK2334470, Cayman Chemical)—10 μM for 4 hours; EGF-100 ng/mL for 1 hour; insulin (Sigma #91077C)—10 μg/ml for 1 hour, F/IBMX (Forskolin, Cayman Chemical/IBMX, Cayman Chemical)—0.1-10 μM for Forskolin and 100 μM for IBMX for 1 hour; L-α-lysophosphatidic acid (LPA) (Sigma #L7260)—0.1-10 μM for 1 hour, sphingosine1-phosphophate (S1P)—1 μM for 1 hour; 12-O-tetradecanoylphorbol-13-acetate (TPA) (#41745; Cell Signaling Technology, Inc., Danvers, Mass., USA)—5 nM for 1 hour; 2-deoxy glucose (#D8375, Sigma-Aldrich Canada Co., Oakville, Ontario, Canada)—25 mM for 1 hour. The results are shown in FIG. **14**.

4. Determine subcellular LATS kinase activity by bioluminescent microscopy.

Using the intermolecular LATS-BS, a new method was developed for the Olympus LV200 Bioluminescence Imager, and LATS kinase activity was visualized and quantified at the individual cell level in cancer cell lines. 3.5 mM D-luciferin was added to the media culturing HEK293A, A549 or MDA-MB231 cells stably expressing LATS-BS at 5-10 min before imaging. Images were captured using Olympus LV200 Bioluminescence Imager with exposure times ranging from 30 seconds (HEK293A) to 10 min (MDA-MB-231, A549). The results are shown in FIG. **15**. The difference in biosensor signal intensity among individual cells represents altered endogenous LATS kinase activity rather than differential LATS-BS expression levels since only the LATS-phosphorylated fraction of LATS-BS should emit bioluminescence. In addition, data showed that both the levels and subcellular localization of LATS-BS bioluminescence (cytoplasm where LATS is expressed) and GFP (control, nucleus/cytoplasm) were different in the same cell. This technology also allowed comparison of the heterogeneity of LATS kinase activity among cancer cell lines by assessing the distribution of luciferase activity. Further, and of particular significance, using biophotonics BLI, LATS kinase activity was detected in vivo in mice. The subcellular activity of LATS kinase can be also visualized by bioluminescent imaging.

5. Measuring LATS kinase activity in mice by in vivo luciferase imaging.

Further, and of particular significance, using biophotonics BLI, LATS kinase activity was detected in vivo in mice. All mouse procedures were approved by the Queen's University Animal Care Committee (UACC) and performed in accordance with institutional policies. To visualize LATS kinase activity in vivo, 12-week-old female BALB/c mice were anesthetized by exposure to 1-3% isoflurane. 3×106 HEK293 cells transfected with an intermolecular LATS-BS alone (LATS−) or together with LATS (LATS+) were suspended in 100 μL of sterile PBS and injected into the mammary fat pad. Two days after the injection, post-surgery mice received 150 mg/kg of D-luciferin (Cedarlane) dissolved in PBS by intraperitoneal injection. Imaging of ventral view was performed using a LightTools Research system (Encinitas, Calif.) dark box and a Hamamatsu ORCA-Flash4.0 V2 digital CMOS camera over a course of 30 minutes to establish optimal peak luciferase activity. Pseudo-colored parametric overlays of BLI with anatomical reference images were dynamically constructed for each individual animal at comparative time points. The bioluminescence (BLI) of the regions of interest (ROI) was then analyzed for total emission flux using Image Pro Plus software. The results are shown in FIG. **16**, where the arrow (right panel) points to the area where high intensity luminescence (red in heatmap) was detected.

6. Identifying novel regulators of LATS by a kinase inhibitor screen.

The intermolecular LATS-BS was used to search for novel kinases regulating Hippo signaling with a small-scale kinase inhibitor screen. The LATS-BS was transfected into HEK293A. Cells were passed into a 384-well plate the following day. 48 hours after transfection, cells were treated with the Tocriscreen Kinase Inhibitor Toolbox (Tocris Bioscience #3514) with each drug administered at 10 μM in DMSO for 4 hours in duplicate. Biosensor activity was then measured by luciferase assay. Fold change ratios were generated by comparing biosensor activity for each drug with that of DMSO-treated controls. The screening schematic and results are shown in FIGS. **17**A and **17**B, respectively. Of 80 kinase inhibitors screened, six kinase inhibitors activated the biosensor (i.e., inhibitors of VEGFR, MEK, GSK-3, PKB/Akt, EGFR, and CDK) while six inhibitors reduced the biosensor signal (i.e., inhibitors of TrkA, Broad, SYK, ATR/ATM, CHK1, and SGK). From these candidate LATS regulators, VEGFR1/2, GSK-3a/b, CDK4, TrkA, SYK, Broad, and SGK are novel. The screen results were confirmed by luciferase assays using the LATS-BS and an STBS-luciferase reporter that measures the transactivating function of YAP/TAZ32. The kinase inhibitors had the opposite effects on LATS-BS and STBS reporter, suggesting that the screen had identified true regulators of Hippo signaling. It is expected that future large-scale screens using the LATS-BS will identify additional new activators or inhibitors of the Hippo signaling pathway.

All cited publications are incorporated herein by reference in their entirety.

Sequences

SEQ ID NO: 1. Human YAP1 (yes-associated protein beta) isoform 2L mRNA (1,401 nucleotides) (accession number: AB567720)

ATGGATCCCGGGCAGCAGCCGCCGCCTCAACCGGCCCCCCAGGGCCAAGGGCAGCCGCCTTCGC

AGCCCCCGCAGGGGCAGGGCCCGCCGTCCGGACCCGGGCAACCGGCACCCGCGGCGACCCAGGC

-continued

GGCGCCGCAGGCACCCCCCGCCGGGCATCAGATCGTGCACGTCCGCGGGGACTCGGAGACCGAC

CTGGAGGCGCTCTTCAACGCCGTCATGAACCCCAAGACGGCCAACGTGCCCCAGACCGTGCCCA

TGAGGCTCCGGAAGCTGCCCGACTCCTTCTTCAAGCCGCCGGAGCCCAAATCCCACTCCCGACA

GGCCAGTACTGATGCAGGCACTGCAGGAGCCCTGACTCCACAGCATGTTCGAGCTCATTCCTCT

CCAGCTTCTCTGCAGTTGGGAGCTGTTTCTCCTGGGACACTGACCCCCACTGGAGTAGTCTCTG

GCCCAGCAGCTACACCCACAGCTCAGCATCTTCGACAGTCTTCTTTTGAGATACCTGATGATGT

ACCTCTGCCAGCAGGTTGGGAGATGGCAAAGACATCTTCTGGTCAGAGATACTTCTTAAATCAC

ATCGATCAGACAACAACATGGCAGGACCCCAGGAAGGCCATGCTGTCCCAGATGAACGTCACAG

CCCCCACCAGTCCACCAGTGCAGCAGAATATGATGAACTCGGCTTCAGCCATGAACCAGAGAAT

CAGTCAGAGTGCTCCAGTGAAACAGCCACCACCCCTGGCTCCCCAGAGCCCACAGGGAGGCGTC

ATGGGTGGCAGCAACTCCAACCAGCAGCAACAGATGCGACTGCAGCAACTGCAGATGGAGAAGG

AGAGGCTGCGGCTGAAACAGCAAGAACTGCTTCGGCAGGCAATGCGGAATATCAATCCCAGCAC

AGCAAATTCTCCAAAATGTCAGGAGTTAGCCCTGCGTAGCCAGTTACCAACACTGGAGCAGGAT

GGTGGGACTCAAAATCCAGTGTCTTCTCCCGGGATGTCTCAGGAATTGAGAACAATGACGACCA

ATAGCTCAGATCCTTTCGTTAACAGTGGCACCTATCACTCTCGAGATGAGAGTACAGACAGTGG

ACTAAGCATGAGCAGCTACAGTGTCCCTCGAACCCCAGATGACTTCCTGAACAGTGTGGATGAG

ATGGATACAGGTGATACTATCAACCAAAGCACCCTGCCCTCACAGCAGAACCGTTTCCCAGACT

ACCTTGAAGCCATTCCTGGGACAAATGTGGACCTTGGAACACTGGAAGGAGATGGAATGAACAT

AGAAGGAGAGGAGCTGATGCCAAGTCTGCAGGAAGCTTTGAGTTCTGACATCCTTAATGACATG

GAGTCTGTTTTGGCTGCCACCAAGCTAGATAAAGAAAGCTTTCTTACATGGTTATAG

SEQ ID NO: 2. Human YAP1 isoform 2L protein (504 amino acids)
MDPGQQPPPQPAPQGQGQPPSQPPQGQGPPSGPGQPAPAATQAAPQAPPAGHQIVHVRGDSETD

LEALFNAVMNPKTANVPQTVPMRLRKLPDSFFKPPEPKSHSRQASTDAGTAGALTPQHVRAHSS

PASLQLGAVSPGTLTPTGVVSGPAATPTAQHLRQSSFEIPDDVPLPAGWEMAKTSSGQRYFLNH

IDQTTTWQDPRKAMLSQMNVTAPTSPPVQQNMMNSASGPLPDGWEQAMTQDGEIYYINHKNKTT

SWLDPRLDPRFAMNQRISQSAPVKQPPPLAPQSPQGGVMGGSNSNQQQQMRLQQLQMEKERLRL

KQQELLRQAMRNINPSTANSPKCQELALRSQLPTLEQDGGTQNPVSSPGMSQELRTMTTNSSDP

FLNSGTYHSRDESTDSGLSMSSYSVPRTPDDFLNSVDEMDTGDTINQSTLPSQQNRFPDYLEAI

PGTNVDLGTLEGDGMNIEGEELMPSLQEALSSDILNDMESVLAATKLDKESFLTWL

SEQ ID NO: 3. Human 14-3-3 protein theta mRNA (738 nucleotides)
(accession number: P27348)
ATGGAGAAGACTGAGCTGATCCAGAAGGCCAAGCTGGCCGAGCAGGCCGAGCGCTACGACGACA

TGGCCACCTGCATGAAGGCAGTGACCGAGCAGGGCGCCGAGCTGTCCAACGAGGAGCGCAACCT

GCTCTCCGTGGCCTACAAGAACGTGGTCGGGGGCCGCAGGTCCGCCTGGAGGGTCATCTCTAGC

ATCGAGCAGAAGACCGACACCTCCGACAAGAAGTTGCAGCTGATTAAGGACTATCGGGAGAAAG

TGGAGTCCGAGCTGAGATCCATCTGCACCACGGTGCTGGAATTGTTGGATAAATATTTAATAGC

CAATGCAACTAATCCAGAGAGTAAGGTCTTCTATCTGAAAATGAAGGGTGATTACTTCCGGTAC

CTTGCTGAAGTTGCGTGTGGTGATGATCGAAAACAAACGATAGATAATTCCCAAGGAGCTTACC

AAGAGGCATTTGATATAAGCAAGAAAGAGATGCAACCCACACACCCAATCCGCCTGGGGCTTGC

TCTTAACTTTTCTGTATTTTACTATGAGATTCTTAATAACCCAGAGCTTGCCTGCACGCTGGCT

AAAACGGCTTTTGATGAGGCCATTGCTGAACTTGATACACTGAATGAAGACTCATACAAAGACA

-continued

GCACCCTCATCATGCAGTTGCTTAGAGACAACCTAACACTTTGGACATCAGACAGTGCAGGAGA

AGAATGTGATGCGGCAGAAGGGGCTGAAAACTAA

SEQ ID NO: 4. Human 14-3-3 protein theta (245 amino acids)
MEKTELIQKAKLAEQAERYDDMATCMKAVTSQGAELSNSERNLLSVAYKNVVGGRRSAWRVISS

IEQKTDTSDKKLQLIKDYREKVESELRSICTTVLELLDKYLIANATHPESKVFYLKMKGDYFRY

LAEVACGDDRKQTIDNSQGAYQEAFDISKKEMQPTHPIRLGLALNFSVFYYEILNNPELACTLA

KTAFDEAIAELDTLNEDSYKDSTLIMQLLRDNLTLWTSDSAGEECDAAEGAEN

SEQ ID NO: 5. Firefly (*Photinus pyralis*) luciferase mRNA (1,653 nucleotides)
ATGGAAGACGCCAAAAACATAAAGAAAGGCCCGGCGCCATTCTATCCGCTGGAAGATGGAACCG

CTGGAGAGCAACTGCATAAGGCTATGAAGAGATACGCCCTGGTTCCTGGAACAATTGCTTTTAC

AGATGCACATATCGAGGTGGACATCACTTACGCTGAGTACTTCGAAATGTCCGTTCGGTTGGCA

GAAGCTATGAAACGATATGGGCTGAATACAAATCACAGAATCGTCGTATGCAGTGAAAACTCTC

TTCAATTCTTTATGCCGGTGTTGGGCGCGTTATTTATCGGAGTTGCAGTTGCGCCCGCGAACGA

CATTTATAATGAACGTGAATTGCTCAACAGTATGGGCATTTCGCAGCCTACCGTGGTGTTCGTT

TCCAAAAAGGGGTTGCAAAAAATTTTGAACGTGCAAAAAAAGCTCCCAATCATCCAAAAAATTA

TTATCATGGATTCTAAAACGGATTACCAGGGATTTCAGTCGATGTACACGTTCGTCACATCTCA

TCTACCTCCCGGTTTTAATGAATACGATTTTGTGCCAGAGTCCTTCGATAGGGACAAGACAATT

GCACTGATCATGAACTCCTCTGGATCTACTGGTCTGCGTAAAGGTGTCGCTCTGCCTCATAGAA

CTGCCTGCGTGAGATTCTCGCATGCCAGAGATCCTATTTTTGGCAATGAAATCATTCCGGATAC

TGCGATTTTAAGTGTTGTTGCATTCCATCACGGTTTTGGAATGTTTACTACACTCGGATATTTG

ATATGTGGATTTCGAGTCGTCTTAATGTATAGATTTGAAGAAGACCTGTTTCTGAGGAGCCTTC

AGGATTACAAGATTCAAAGTGCGCTGCTGGTGCCAACCCTATTCTCCTTCTTCGCCAAAAGCAC

TCTGATTGACAAATACGATTTATCTAATTTACACGAAATTGCTTCTGGTGGCGCTCCCCTCTCT

AAGGAAGTCGGGGAAGCGGTTGCCAAGAGGTTCCATCTGCCAGGTATCAGGCAAGGATATGGGC

TCACTGAGACTACATCAGCTATTCTGATTACACCCGAGGGGGATGATAAACCGGGCGCGGTCGG

TAAAGTTGTTCCATTTTTTGAAGCGAAGGTTGTGGATCTGGATACCGGGAAAACGCTGGGCGTT

AATCAAAGAGGCGAACTGTGTGTGAGAGGTCCTATGATTATGTCCGGTTATGTAAACAATCCGG

AAGCGACCAACGCCTTGATTGACAAGGATGGATGGCTACATTCTGGAGACATAGCTTACTGGGA

CGAAGACGAACACTTCTTCATCGTTGACCGCCTGAAGTCTCTGATTAAGTACAAAGGCTATCAG

GTGGCTCCCGCTGAATTGGAATCCATCTTGCTCCAACACCCCAACATCTTCGACGCAGGTGTCG

CAGGTCTTCCCGACGATGACGCCGGTGAACTTCCCGCCGCCGTTGTTGTTTTGGAGCACGGAAA

GACGATGACGGAAAAAGAGATCGTGGATTACGTCGCCAGTCAAGTAACAACCGCGAAAAAGTTG

CGCGGAGGAGTTGTGTTTGTGGACGAAGTACCGAAAGGTCTTACCGGAAAACTCGACGCAAGAA

AAATCAGAGAGATCCTCATAAAGGCCAAGAAGGGCGGAAAGATCGCCGTGTAA

SEQ ID NO: 6. Firefly (*Photinus pyralis*) luciferase protein (555 amino acids)
MEDAKNIKKGPAPFYPLEDGTAGEQLHKAMKRYALVPGTIAFTDAHIEVDITYAEYFEMSVRLA

EAMKRYGLNTNHRIVVCSENSLQFFMPVLGALFIGVAVAPANDIYNERELLNSMGISQPTVVFV

SKKGLQKILNVQKKLPIIQKIIIMDSKTDYQGFQSMYTFVTSHLPPGFKEYDFVPESFDRDKTI

ALIMNSSGSTGLPKGVALPHRTACVRFSHARDPIFGNQIIPDTAILSVVPFHHGFGMFTTLGYL

ICGFRVVLMYRFEEELFLRSLQDYKIQSALLVPTLFSFFAKSTLIDKYDLSNLHEIASGGAPLS

KEVGEAVAKRFHLPGIRQGYGLTETTSAILITPEGDDKPGAVGKVVPFFEAKVVDLDTGKTLGV

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NQRGELCVRGPMIMSGYVNNPEATNALIDKDGWLHSGDIAYWDEDEHFFIVDRLKSLIKYKGYQ

VAPAELESILLQHPNIFDAGVAGLPDDDAGELPAAVVVLEKGKTMTEKEIVDYVASQVTTAKKL

RGGVVFVDEVPKGLTGKLDARKIREILIKAKKGGKIAV

SEQ ID NO: 7. YAP15 S127 wildtype (WT) protein fragment (15 amino acids)
PQHVRHASSPASLQL

SEQ ID NO: 8. YAP15 A127 mutant protein fragment (15 amino acids)
PQHVRHAASPASLQL

SEQ ID NO: 9. pcDNA3.1/hygro(+) vector (5,597 nucleotides)
GACGGATCGGGAGATCTCCCGATCCCCTATGGTGCACTCTCAGTACAATCTGCTCTGATGCCGC

ATAGTTAAGCCAGTATCTGCTCCCTGCTTGTGTGTTGGAGGTCGCTGAGTAGTGCGCGAGCAAA

ATTTAAGCTACAACAAGGCAAGGCTTGACCGACAATTGCATGAAGAATCTGCTTAGCGTTAGGC

GTTTTGCGCTGCTTCGCGATGTACGGGCCAGATATACGCGTTGACATTGATTATTGACTAGTTA

TTAATAGTAATCAATTACGGGGTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAA

CTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTGAATAATGA

CGTATGTTCCCATAGTAACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACG

GTAAACTGCCCACTTGGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTC

AATGACGGTAAATGGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTT

GGCAGTACATCTACGTATTAGTCATCGCTATTACCATGGTGATGCGGTTTTGGCAGTACATCAA

TGGGCGTGGATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGACGTCAATGGG

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CGCAAATGGGCGGTAGGCGTGTACGGTGGGAGGTCTATATAAGCAGAGCTCTCTGGCTAACTAG

AGAACCCACTGCTTACTGGCTTATCGAAATTAATACGACTCACTATAGGGAGACCCAAGCTGGC

TAGCGTTTAAACTTAAGCTTGGTACCGAGCTCGGATCCACTAGTCCAGTGTGGTGGAATTCTGC

AGATATCCAGCACAGTGGCGGCCGCTCGAGTCTAGAGGGCCCGTTTAAACCCGCTGATCAGCCT

CGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCCTCCCCCGTGCCTTCCTTGACCCT

GGAAGGTGCCACTCCCACTGTCCTTTCCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGT

AGGTGTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACA

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CGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTCGCTTTCTTCCCTTCCT

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TTTGCCGATTTCGGCCTATTGGTTAAAAAATGAGCTGATTTAACAAAAATTTAACGCGAATTAA

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TCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTTTTTTAT

TTATGCAGAGGCCGAGGCCGCCTCTGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTT

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ACCGAACTGCCCGCTGTTCTGCAGCCGGTCGCGGAGGCCATGGATGCGATCGCTGCGGCCGATC

TTAGCCAGACGAGCGGGTTCGGCCCATTCGGACCGCAAGGAATCGGTCAATACACTACATGGCG

TGATTTCATATGCGCGATTGCTGATCCCCATGTGTATCACTGGCAAACTGTGATGGACGACACC

GTCAGTGCGTCCGTCGCGCAGGCTCTCGATGAGCTGATGCTTTGGGCCGAGGACTGCCCCGAAG

TCCGGCAGCTCGTGCACGCGGATTTCGGCTCCAACAATGTCCTGACGGACAATGGCCGGATAAC

AGCGGTCATTGACTGGAGCGAGGCGATGTTCGGGGATTCCCAATACGAGGTCGCCAACATGTTC

TTCTGGAGGCCGTGGTTGGCTTGTATGGAGCAGCAGACGCGCTACTTCGAGCGGAGGCATCCGG

AGCTTGCAGGATCGCCGCGGCTCCGGGCGTATATGCTCCGCATTGGTCTTGACCAACTCTATCA

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CGATCCGGAGCCGGGACTGTCGGGCGTACAGAAATCGCCCGCAGAAGCGCGGCCGTGTGGACCG

ATGGCTGTGTAGAAGTACTCGCCGATAGTGGAAAGCGACGCCCCAGCACTCGTCCGAGGGCAAA

GGAATAGCACGTGCTACGAGATTTCGATTCCACCGCCGCCTTCTATGAAAGGTTGGGCTTCGGA

ATCGTTTTCCGGGACGCCGGCTGGATGATCCTCCAGCGCGGGGATCTGATGCTGGAGTTCTTCG

CCCACCCCAACTTGTTTATTGCAGCTTATAATGGTTACAAATAAAGCAATAGCATCACAAATTT

CACAAATAAAGCATTTTTTTCACTGCATTCTAGTTGTGGTTTGTCCAAACTCATCAATGTATCT

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CCTGTTCCGACCCTGCCGCTTACCGGATACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTGGCGC

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AGTATTTGGTATCTGCGCTCTGCTGAAGCCAGTTACCTTCGGAAAAAGAGTTGGTAGCTCTTGA

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AAAAAGGATCTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGCTCAGTGGAACGAAAA

CTCACGTTAAGGGATTTTGGTCATGAGATTATCAAAAAGGATCTTCACCTAGATCCTTTTAAAT

TAAAAATGAAGTTTTAAATCAATCTAAAGTATATATGAGTAAACTTGGTCTGACAGTTACCAAT

GCTTAATCAGTGAGGCACCTATCTCAGCGATCTGTCTATTTCGTTCATCCATAGTTGCCTGACT

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CATGATCCCCCATGTTGTGCAAAAAAGCGGTTAGCTCCTTCGGTCCTCCGATCGTTGTCAGAAG

TAAGTTGGCCGCAGTGTTATCACTCATGGTTATGGCAGCACTGCATAATTCTCTTACTGTCATG

CCATCCGTAAGATGCTTTTCTGTGACTGGTGAGTACTCAACCAAGTCATTCTGAGAATAGTGTA

TGCGGCGACCGAGTTGCTCTTGCCCGGCGTCAATACGGGATAATACCGCGCCACATAGCAGAAC

TTTAAAAGTGCTCATCATTGGAAAACGTTCTTCGGGGCGAAAACTCTCAAGGATCTTACCGCTG

TTGAGATCCAGTTCGATGTAACCCACTCGTGCACCCAACTGATCTTCAGCATCTTTTACTTTCA

CCAGCGTTTCTGGGTGAGCAAAAACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGGCGAC

ACGGAAATGTTGAATACTCATACTCTTCCTTTTTCAATATTATTGAAGCATTTATCAGGGTTAT

TGTCTCATGAGCGGATACATATTTGAATGTATTTAGAAAAATAAACAAATAGGGGTTCCGCGCA

CATTTCCCCGAAAAGTGCCACCTGAGGTC

SEQ ID NO: 10. B1-Kozak-Nluc-F primer (41 nucleotides)
CTGGATCCGCCGCCACCATGGAAGACGCCAAAAACATG

SEQ ID NO: 11. Nluc-416-Yap-15-S127-(GGAGG)-R primer (84 nucleotides)
TTACAACTGCAGAGAAGCTGGAGAGGAATGAGCTCGAACATGCTGTGGGCCTCCAGCTCCTCCT

CCATCCTTGTCAATCAAGGC

SEQ ID NO: 12. N1-Yap-5-Overlapping PCR-R primer (36 nucleotides)
ATGATACTGCGGCCGCTTACAACTGCAGAGAAGCTG

SEQ ID NO: 13. B1-Kozak-14-3-3-F primer (38 nucleotides)
CTGGATCCGCCGCCACCATGGAGAAGACTGAGCTGATC

SEQ ID NO: 14. (GGGGS)2-14-3-3-R primer (51 nucleotides)
ACTACCTCCTCCTCCACTACCTCCTCCTCCGTTTTCAGCCCCTTCTGCCGC

SEQ ID NO: 15. (GGGGS)2-Cluc394-F primer (39 nucleotides)
GGTAGTGGAGGAGGAGGTAGTGGTCCTATGATTATGTCC

SEQ ID NO: 16. N1-Cluc-R primer (34 nucleotides)
ATGAAACTGCGGCCGCTTACACGGCGATCTTTCC

SEQ ID NO: 17. Nluc398-15-S127-(GGAGG)-R primer (81 nucleotides)
CAACTGCAGAGAAGCTGGAGAGGAATGAGCTCGAACATGCTGTGGGCCTCCAGCTCCTCCCATA

ATCATAGGACCTCTCAC

SEQ ID NO: 18. Yap15-S127-Cluc394-F primer (42 nucleotides)
TCTCCAGCTTCTCTGCAGTTGGGTCCTATGATTATGTCCGGT

SEQ ID NO: 19. N1-Yap15-S127-Cluc443 (engineered C-terminus of luciferase)-R primer (86 nucleotides)
ATGAAACTGCGGCCGCTTACAACTGCAGAGAAGCTGGAGAGGAATGAGCTCGAACATGCTGTGG

CTTCTTGGCCTTTATGAGGATC

SEQ ID NO: 20. EcoR1-YAP-S127-BglII-S primer (55 nucleotides)
AATTCACCACAGCATGTTCGAGGTCATTCCTCTCCAGCTTCTCTGCAGTTGTGAA

SEQ ID NO: 21. ECoR1-YAP-S127-BglII-AS primer (55 nucleotides)
GATCTTCACAACTGCAGAGAAGCTGGAGAGGAATGAGCTCGAACATGCTGTGGTG

SEQ ID NO: 22. EcoR1-YAP-A127-BglII-S primer (55 nucleotides)
AATTCACCACAGCATGTTCGAGCTCATGCGTCTCCAGCTTCTCTGCAGTTGTGAA

SEQ ID NO: 23. ECoR1-YAP-A127-BglII-AS primer (55 nucleotides)
GATCTTCACAACTGCAGAGAAGCTGGAGACGCATGAGCTCGAACATGCTGTGGTG

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SEQ ID NO: 24. BglII-14-3-3-F primer (31 nucleotides)
GGAAGATCTAATGGAGAAGACTGAGCTGATC

SEQ ID NO: 25. ECoR1-14-3-3-R primer (34 nucleotides)
CGCCGGAATTCCCGTTTTCAGCCCCTTCTGCCGC

SEQ ID NO: 26. pBiT 1.1 N (TK-Larg BiT) whole vector (3,858 nucleotides)
GGCCTAACTGGCCGGTACCTGAGTCTAAATGAGTCTTCGGACCTCGCGGGGGCCGCTTAACCGG

TGGTTAGGGTTTGTCTGACGCGGGGGGAGGGGGAAGGAACGAAACACTCTCATTCGGAGGCGGC

TCGGGGTTTGGTCTTGGTGGCCACGGGCACGCAGAAGAGCGCCGCGATCCTCTTAAGCACCCCC

CCGCCCTCCGTGGAGGCGGGGGTTTGGTCGGCGGGTGGTAACTGGCGGGCGGCTGACTCGGGCG

GGTCGCGCGCCCCAGAGTGTGACCTTTTCGGTCTGCTCGCAGACCCCCGGGCGGCGCCGCCGCG

GCGGCGACGGGCTCGCTGGGTCCTAGGCTCCATGGGGACCGTATACGTGGACAGGCTCTGGAGC

ATCCGCACGACTGCGGTGATATTAGCGGAGACCTTCTGCGGGACGAGCCGGGTCACGCGGCTGA

CGCGGAGCGTCGGTTGGGCGACAAACAGCAGGACGGGGCACAGGTACACTATCTTGTCACCCGG

AGGCGCGAGGGACTGCAGGAGCTTCAGGGAGTGGCGCAGCTGCTTCATCCCCGTGGCCCGTTGC

TCGCGTTTGCTGGCGGTGTCCCCGGAAGAAATATATTTGCATGTCTTTAGTTCTATGATGACAC

AAACCCCGCCCAGCGTCTTGTCATTGGCGAAGTCGAACACGCAGATGCAGTCGGGGCGGCGCGG

TCCCAGGTCCACTTCGCATATTAAGGTGACGCGTGTGGCCTCGAACACCGAGCGACCCTGCAGC

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CAAATGGCCCAGATCGAAGAGGTGTTTAAGGTGGTGTACCCTGTGGATGATCATCACTTTAAGG

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CTTCTTTATCATGCAACTCGTAGGACAGGTGCCGGCAGCGCTCTTCCGCTTCCTCGCTCACTGA

CTCGCTGCGCTCGGTCGTTCGGCTGCGGCGAGCGGTATCAGCTCACTCAAAGGCGGTAATACGG

TTATCCACAGAATCAGGGGATAACGCAGGAAAGAACATGTGAGCAAAAGGCCAGCAAAAGGCCA

GGAACCGTAAAAAGGCCGCGTTGCTGGCGTTTTTCCATAGGCTCCGCCCCCCTGACGAGCATCA

CAAAAATCGACGCTCAAGTCAGAGGTGGCGAAACCCGACAGGACTATAAAGATACCAGGCGTTT

CCCCCTGGAAGCTCCCTCGTGCGCTCTCCTGTTCCGACCCTGCCGCTTACCGGATACCTGTCCG

CCTTTCTCCCTTCGGGAAGCGTGGCGCTTTCTCATAGCTCACGCTGTAGGTATCTCAGTTCGGT

GTAGGTCGTTCGCTCCAAGCTGGGCTGTGTGCACGAACCCCCCGTTCAGCCCGACCGCTGCGCC

TTATCCGGTAACTATCGTCTTGAGTCCAACCCGGTAAGACACGACTTATCGCCACTGGCAGCAG

CCACTGGTAACAGGATTAGCAGAGCGAGGTATGTAGGCGGTGCTACAGAGTTCTTGAAGTGGTG

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CGTCTCTCAAGGATAAGTAAGTAATATTAAGGTACGGGAGGTATTGGACAGGCCGCAATAAAAT

ATCTTTATTTTCATTACATCTGTGTGTTGGTTTTTTGTGTGAATCGATAGTACTAACATACGCT

CTCCATCAAAACAAAACGAAACAAAACAAACTAGCAAAATAGGCTGTCCCCAGTGCAAGTGCAG

GTGCCAGAACATTTCTCT

SEQ ID NO: 27. pBiT 2.1 C (TK-SmBiT) whole vector (3,423 nucleotides)

GGCCTAACTGGCCGGTACCTGAGTCTAAATGAGTCTTCGGACCTCGCGGGGGCCGCTTAAGCGG

TGGTTAGGGTTTGTCTGACGCGGGGGGAGGGGGAAGGAACGAAACACTCTCATTCGGAGGCGGC

TCGGGGTTTGGTCTTGGTGGCCACGGGCACGCAGAAGAGCGCCGCGATCCTCTTAAGCACCCCC

CCGCCCTCCGTGGAGGCGGGGGTTTGGTCGGCGGGTGGTAACTGGCGGGCCGCTGACTCGGGCG

GGTCGCGCGCCCCAGAGTGTGACCTTTTCGGTCTGCTCGGAGACCCCCGGGCGGCGCCGCCGCG

GCGGCGACGGGCTCGCTGGGTCCTAGGCTCCATGGGGACCGTATACGTGGACAGGCTCTGGAGC

ATCCGCACGACTGCGGTGATATTACCGGAGACCTTGTGCGGGACGAGCCGGGTCACGCGGCTGA

CGCGGAGCGTCCGTTGGGCGACAAACACCAGGACGGGGCACAGGTACACTATCTTGTCACCCGG

AGGCGCGAGGGACTGCAGGAGCTTCAGGGAGTGGCGCAGCTGCTTCATCCCCGTGGCCCGTTGC

TCGCGTTTGCTGGCGGTGTCCCCGGAAGAAATATATTTGCATGTCTTTAGTTCTATGATGACAC

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GAGGGCCGAGCGAAGAAGTGGTCCTGCTACTTTGTCCGCCTCCATCCAGTCTATGAGCTGCTGT

CGTGATGCTAGAGTAAGAAGTTCGCCAGTGAGTAGTTTCCGAAGAGTTGTGGCCATTGCTACTG

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TGCCGCTATTGAGATCCAGTTCGATATAGCCCACTCTTGCACCCAGTTGATCTTCAGCATCTTT

TACTTTCACCAGCGTTTCGGGGTGTGCAAAAACAGGCAAGCAAAATGCCGCAAAGAAGGGAATG

AGTGCGACACGAAAATGTTGGATGCTCATACTCGTCCTTTTTCAATATTATTGAAGCATTTATC

AGGGTTACTAGTACGTCTCTCAAGGATAAGTAAGTAATATTAAGGTACGGGAGGTATTGGACAG

GCCGCAATAAAATATCTTTATTTTCATTACATCTGTGTGTTGGTTTTTTGTGTGAATCGATAGT

ACTAACATACGCTCTCCATCAAAACAAAACGAAACAAAACAAACTAGCAAAATAGGCTGTCCCC

AGTGCAAGTGCAGGTGCCAGAACATTTCTCT

SEQ ID NO: 28. NdeI-LgBiT-YAP15-F primer (38 nucleotides)
GGAATTCATATGATGGTCTTCACACTCGAAGATTTCGT

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SEQ ID NO: 29. B1-LgBiT-YAP15-R primer (40 nucleotides)
CGCGGGATCCTTACAACTGCAGAGAAGCTGGAGAGGAATG

SEQ ID NO: 30. B1-LgBiT-YAP15A127-R primer (43 nucleotides)
CGCGGGATCCTTACAACTGCAGAGAAGCTGGAGACGCATGAGC

SEQ ID NO: 31. NdeI-14-3-3-SmBiT-F primer (38 nucleotides)
GGAATTCATATGATGGAGAAGACTGAGCTGATCCAGAA

SEQ ID NO: 32. B1-14-3-3-SmBiT-R primer (40 nucleotides)
CGCGGGATCCTTACAGAATCTCCTCGAACAGCCGGTAGCC

SEQ ID NO: 33. pET 16b (6 his N-terminal) whole vector (5,711 nucleotides)
TTCTCATGTTTGACAGCTTATCATCGATAAGCTTTAATGCGGTAGTTTATCACAGTTAAATTGC

TAACGCAGTCAGGCACCGTGTATGAAATCTAACAATGCGCTCATCGTCATCCTCGGCACCGTCA

CCCTGGATGCTGTAGGCATAGGCTTGGTTATGCCGGTACTGCCGGGCCTCTTGCGGGATATCCG

GATATAGTTCCTCCTTTCAGCAAAAAACCCCTCAAGACCCGTTTAGAGGCCCCAAGGGGTTATG

CTAGTTATTGCTCAGCGGTGGCAGCAGCCAACTCAGCTTCCTTTCGGGCTTTGTTAGCAGCCGG

ATCCTCGAGCATATGACGACCTTCGATATGGCCGCTGCTGTGATGATGATGATGATGATGATGA

TGATGGCCCATGGTATATCTCCTTCTTAAAGTTAAACAAAATTATTTCTAGAGGGGAATTGTTA

TCCGCTCACAATTCCCCTATAGTGAGTCGTATTAATTTCGCGGGATCGAGATCTCGATCCTCTA

CGCCGGACGCATCGTGGCCGGCATCACCGGCGCCACAGGTGCGGTTGCTGGCGCCTATATCGCC

GACATCACCGATGGGGAAGATCGGGCTCGCCACTTCGGGCTCATGAGCGCTTGTTTCGCCGTGG

GTATGGTGGCAGGCCCCGTGGCCGGGGGACTGTTGGGCGCCATCTCCTTGCATGCACCATTCCT

TGCGGCGGCGGTGCTCAACGGCCTCAACCTACTACTGGGCTGCTTCCTAATGCAGGAGTCGCAT

AAGGGAGAGCGTCGAGATCCCGGACACCATCGAATGGCGCAAAACCTTTCGCGGTATGGCATGA

TAGCGCCCGGAAGAGAGTCAATTCAGGGTGGTGAATGTGAAACCAGTAACGTTATACGATGTCG

CAGAGTATGCCGGTGTCTCTTATCAGACCGTTTCCCGCGTGGTGAACCAGGCCAGCCACGTTTC

TGCGAAAACGCGGGAAAAAGTGGAAGCGGCGATGGCGGAGCTGAATTACATTCCCAACCGCGTG

GCACAACAACTGGCGGGCAAACAGTCGTTGCTGATTGGCGTTGCCACCTCCAGTCTGGCCCTGC

ACGCGCCGTCGCAAATTGTCGCGGCGATTAAATCTCGCGCCGATCAACTGGGTGCCAGCGTGGT

GGTGTCGATGGTAGAACGAAGCGGCGTCGAAGCCTGTAAAGCGGCGGTGCACAATCTTCTCGCG

CAACGCGTCAGTGGGCTGATCATTAACTATCCGCTGGATGACCAGGATGCCATTGCTGTGGAAG

CTGCCTGCACTAATGTTCCGGCGTTATTTCTTGATGTCTCTGACCAGACACCCATCAACAGTAT

TATTTTCTCCCATGAAGACGGTACGCGACTGGGCGTGGAGCATCTGGTCGCATTGGGTCACCAG

CAAATCGCGCTGTTAGCGGGCCCATTAAGTTCTGTCTCGGCGCGTCTGCGTCTGGCTGGCTGGC

ATAAATATCTCACTCGCAATCAAATTCAGCCGATAGCGGAACGGGAAGGCGACTGGAGTGCCAT

GTCCGGTTTTCAACAAACCATGCAAATGCTGAATGAGGGCATCGTTCCCACTGCGATGCTGGTT

GCCAACGATCAGATGGCGCTGGGCGCAATGCGCGCCATTACCGAGTCCGGGCTGCGCGTTGGTG

CGGATATCTCGGTAGTGGGATACGACGATACCGAAGACAGCTCATGTTATATCCCGCCGTTAAC

CACCATCAAACAGGATTTTCGCCTGCTGGGGCAAACCAGCGTGGACCGCTTGCTGCAACTCTCT

CAGGGCCAGGCGGTGAAGGGCAATCAGCTGTTGCCCGTCTCACTGGTGAAAAGAAAAACCACCC

TGGCGCCCAATACGCAAACCGCCTCTCCCCGCGCGTTGGCCGATTCATTAATGCAGCTGGCACG

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GCGCGGGGCATGACTATCGTCGCCGCACTTATGACTGTCTTCTTTATCATGCAACTCGTAGGAC

AGGTGCCGGCAGCGCTCTGGGTCATTTTCGGCGAGGACCGCTTTCGCTGGAGCGCGACGATGAT

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ACGTCTTGCTGGCGTTCGCGACGCGAGGCTGGATGGCGTTCCCCATTATGATTCTTCTCGCTTC

CGGCGGCATCGGGATGCCCGCGTTGCAGGCCATGCTGTCCAGGCAGGTAGATGACGACCATCAG

GGACAGCTTCAAGGATCGCTCGCGGCTCTTACCAGCCTAACTTCGATCACTGGACCGCTGATCG

TCACGGCGATTTATGCCGCCTCGGCGAGCACATGGAACGGGTTGGCATGGATTGTAGGCGCCGC

CCTATACCTTGTCTGCCTCCCCGCGTTGCGTCGCGGTGCATGGAGCCGGGCCACCTCGACCTGA

ATGGAAGCCGGCGGCACCTCGCTAACGGATTCACCACTCCAAGAATTGGAGCCAATCAATTCTT

GCGGAGAACTGTGAATGCGCAAACCAACCCTTGGCAGAACATATCCATCGCGTCCGCCATCTCC

AGCAGCCGCACGCGGCGCATCTCGGGCAGCGTTGGGTCCTGGCCACGGGTGCGCATGATCGTGC

TCCTGTCGTTGAGGACCCGGCTAGGCTGGCGGGGTTGCCTTACTGGTTAGCAGAATGAATCACC

GATACGCGAGCGAACGTGAAGCGACTGCTGCTGCAAAACGTCTGCGACCTGAGCAACAACATGA

ATGGTCTTCGGTTTCCGTGTTTCGTAAAGTCTGGAAACGCGGAAGTCAGCGCCCTGCACCATTA

TGTTCCGGATCTGCATCGCAGGATGCTGCTGGCTACCCTGTGGAACACCTACATCTGTATTAAC

GAAGCGCTGGCATTGACCCTGAGTGATTTTTCTCTGGTCCCGCCGCATCCATACCGCCAGTTGT

TTACCCTCACAACGTTCCAGTAACCGGGCATGTTCATCATCAGTAACCCGTATCGTGAGCATCC

TCTCTCGTTTCATCGGTATCATTACCCCCATGAACAGAAATCCCCCTTACACGGAGGCATCAGT

GACCAAACAGGAAAAAACCGCGCTTAACATGGCCCGCTTTATCAGAAGCCAGACATTAACGCTT

CTGGAGAAACTCAACGAGCTGGACGCGGATGAACAGGCAGACATCTGTGAATCGCTTCACGACC

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CATGCAGCTCCCGGAGACGGTCACAGCTTGTCTGTAAGCGGATGCCGGGAGCAGACAAGCCCGT

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GCGGAGTGTATACTGGCTTAACTATGCGGCATCAGAGCAGATTGTACTGAGAGTGCACCATATA

TGCGGTGTGAAATACCGCACAGATGCGTAAGGAGAAAATACCGCATCAGGCGCTGTTCCGGTTC

CTCGCTCACTGACTCGCTGCGCTCGGTCGTTCGGCTGCGGCGAGCGGTATCAGCTCACTCAAAG

GCGGTAATACGGTTATCCACAGAATCAGGGGATAACGCAGGAAAGAACATGTGAGCAAAAGGCC

AGCAAAAGGCCAGGAACCGTAAAAAGGCCGCGTTGCTGGCGTTTTTCCATAGGCTCCGCCCCCC

TGACGAGCATCACAAAAATCGACGCTCAAGTCAGAGGTGGCGAAACCCGACAGGACTATAAAGA

TACCAGGCGTTTCCCCCTGGAAGCTCCCTCGTGCGCTCTCCTGTTCCGACCCTGCCGCTTACCG

GATACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTGGCGCTTTCTCATAGCTCACGCTGTAGGTA

TCTCAGTTCGGTGTAGGTCGTTCGCTCCAAGCTGGGCTGTGTGCACGAACCCCCCGTTCAGCCC

GACCGCTGCGCCTTATCCGGTAAGTATGGTCTTGAGTCCAACCCGGTAAGACACGACTTATCGC

CACTGGCAGCAGCCACTGGTAACAGGATTAGCAGAGCGAGGTATGTAGGCGGTGCTACAGAGTT

CTTGAAGTGGTGGCCTAACTACGGCTACACTAGAAGGACAGTATTTGGTATCTGCGCTCTGCTG

AAGCCAGTTACCTTCGGAAAAAGAGTTGGTAGCTCTTGATCCGGCAAACAAACCACCGCTGGTA

GCGGTGGTTTTTTTGTTTGCAAGCAGCAGATTACGCGCAGAAAAAAAGGATCTCAAGAAGATCC

TTTGATCTTTTCTACGGGGTCTGACGCTCAGTGGAACGAAAACTCACGTTAAGGGATTTTGGTC

ATGAGATTATCAAAAAGGATCTTCACCTAGATCCTTTTAAATTAAAAATGAAGTTTTAAATCAA

TCTAAAGTATATATGAGTAAACTTGGTCTGACAGTTACCAATGCTTAATCAGTGAGGCACCTAT

CTGAGCGATCTGTCTATTTCGTTCATCCATAGTTGCCTGACTGCCCGTCGTGTAGATAACTACG

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ATACGGGAGGGCTTACCATCTGGCCCCAGTGCTGCAATGATACCGGGAGACCCACGCTCACCGG

CTCCAGATTTATCAGCAATAAACCAGCCAGCCGGAAGGGCCGAGCGCAGAAGTGGTCCTGCAAC

TTTATCCGCCTCCATCCAGTCTATTAATTGTTGCCGGGAAGCTAGAGTAAGTAGTTCGCCAGTT

AATAGTTTGCGCAACGTTGTTGCCATTGCTGCAGGCATCGTGGTGTCACGCTCGTCGTTTGGTA

TGGCTTCATTCAGCTCCGGTTCCCAACGATCAAGGCGAGTTACATGATCCCCCATGTTGTGCAA

AAAAGCGGTTAGCTCCTTCGGTCCTCCGATCGTTGTCAGAAGTAAGTTGGCCGCAGTGTTATCA

CTCATGGTTATGGCAGCACTGCATAATTCTCTTACTGTCATGCCATCCGTAAGATGCTTTTCTG

TGACTGGTGAGTACTCAACCAAGTCATTCTGAGAATAGTGTATGCGGCGACCGAGTTGCTCTTG

CCCGGCGTCAACACGGGATAATACCGCGCCACATAGCAGAACTTTAAAAGTGCTCATCATTGGA

AAACGTTCTTCGGGGCGAAAACTCTCAAGGATCTTACCGCTGTTGAGATCCAGTTCGATGTAAC

CCACTCGTGCACCCAACTGATCTTCAGCATCTTTTACTTTCAGCAGCGTTTCTGGGTGAGCAAA

AACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGGCGACACGGAAATGTTGAATACTCATA

CTCTTCCTTTTTCAATATTATTGAAGCATTTATCAGGGTTATTGTCTCATGAGCGGATACATAT

TTGAATGTATTTAGAAAAATAAACAAATAGGGGTTCCGCGCACATTTCCCCGAAAAGTGCCACC

TGACGTCTAAGAAACCATTATTATCATGACATTAACCTATAAAAATAGGCGTATCACGAGGCCC

TTTCGTCTTCAAGAA
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SEQ ID NO: 34. B1-Kozak-LgBiT-F primer (41 nucleotides)
CTGGATCCGCCGCCACCATGGTCTTTCACACTCGAAGATTTC

SEQ ID NO: 35. LgBiT-(GS)-R primer (54 nucleotides)
ACCGCTCGAGCCTCCACCTCCGCTCCCGCCACCACCGGAACTCCCACTGTTGAT

SEQ ID NO: 36. (GS)-YAP50-F primer (69 nucleotides)
GGGAGTTCCGGTGGTGGCGGGAGCGGAGGTGGAGGCTCGAGCGGTGCCGGGCATCAGATCGTGC

ACGTC

SEQ ID NO: 37. N1-YAP171-Flag-R primer (63 nucleotides)
ATGAAACTGCGGCCGCCTTGTCGTCATCGTCTTTGTAGTCTACATCATCAGGTATCTCAAAAG

SEQ ID NO: 38. B1-YAP50-F primer (32 nucleotides)
CTGGATCCGCCGGGCATCAGATCGTGCACGTC

SEQ ID NO: 39. (GS)-YAP171-R primer (68 nucleotides)
ACCTGACGACCCTCCACCTCCGCTCCCGCCACCACCGCTCGAGCCTACATCATCAGGTATCTCA

AAAG

SEQ ID NO: 40. (GS)-LgBiT-F primer (66 nucleotides)
GGCTCGAGCGGTGGTGGCGGGAGCGGAGGTGGAGGGTCGTCAGGTGTCTTCACACTCGAAGATT

TC

SEQ ID NO: 41. N1-LgBiT-R primer (43 nucleotides)
ATGAAACTGCGGCCGCTTAACTGTTGATGGTTACTCGGAACAG

SEQ ID NO: 42. B1-Kozak-SmiBiT-(GS)-F primer (98 nucleotides)
CTGGATCCGCCGCCACCATGGTGACCGGCTACCGGCTGTTCGAGGAGATTCTCGGGAGTTCCGG

TGGTGGCGGGAGCGGAGGTGGAGGCTCGAGCGGT

SEQ ID NO: 43. N1-SmBiT-(GS)-R primer (97 nucleotides)
ATGAAACTGCGGCCGCTTAGAGAATCTCCTCGAACAGCCGGTAGCCGGTCACACCTGACGACCC

TCCACCTCCGCTCCCGCCACCACCGCTCGAGCC

SEQ ID NO: 44. (GS)-TEAD-194-F primer (73 nucleotides)
GGGAGTTCCGGTGGTGGCGGGAGCGGAGGTGGAGGCTCGAGCGGTGAGCCTGCATCGGCCCCAG

CTCCCTCAG

SEQ ID NO: 45. N1-TEAD411-Myc-R primer (73 nucleotides)
ATGAAACTGCGGCCGCTTACAGATCCTCTTCTGAGATGAGTTTTTGTTCATTTGAAACTTCAAA

CACACAGGC

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SEQ ID NO: 46. B1-TEAD194-F primer (36 nucleotides)
CTGGATCCGAGCCTGCATCGGCCCCAGCTCCCTCAG

SEQ ID NO: 47. GS-TEAD-411-R primer (69 nucleotides)
ACCTGACGACCCTCCACCTCCGCTCCCGCCACCACCGCTCGAGCCATTTGAAACTTCAAACACA

CAGGC

SEQ ID NO: 48. (GS)-TEAD194-F primer (73 nucleotides)
GGGAGTTCCGGTGGTGGCGGGAGCGGAGGTGGAGGCTCGAGCGGTGAGCCTGCATCGGCCCCAG

CTCCCTGAG

SEQ ID NO: 49. TEAD1_HUMAN transcriptional enhancer factor TEF-1 (accession number P28347) mRNA (1,281 nucleotides)
ATTGAGCCCAGCAGCTGGAGCGGCAGTGAGAGCCCTGCCGAAAACATGGAAAGGATGAGTGACT

CTGCAGATAAGCCAATTGACAATGATGCAGAAGGGGTCTGGAGCCCCGACATCGAGCAAACCTT

TCAGGAGGCCCTGGCTATCTATCCACCATGTGGGAGGAGGAAAATCATCTTATCAGACGAAGGC

AAAATGTATGGTAGGAATGAATTGATAGCCAGATACATCAAACTCAGGACAGGCAAGACGAGGA

CCAGAAAACAGGTGTCTAGTCACATTCAGGTTCTTGCCAGAAGGAAATCTCGTGATTTTCATTC

CAAGCTAAAGGATCAGACTGCAAAGGATAAGGCCCTGCAGCACATGGCGGCCATGTCCTCAGCC

CAGATCGTCTCGGCCACTGCGATTCATAAGAAGCTGGGGCTGCCTGGGATTCCACGCCCGACCT

TCCCAGGGGCGCCGGGGTTCTGGCCGGGAATGATTCAAACAGGGCAGCCAGGATCCTCACAAGA

CGTCAAGCCTTTTGTGCAGCAGGCCTACCCCATCCAGCCAGCGGTCACAGCCCCCATTCCAGGG

TTTGAGCCTGCATCGGCCCCAGCTCCCTCAGTCCCTGCCTGGCAAGGTCGCTCCATTGGCACAA

CCAAGCTTCGCCTGGTGGAATTTTCAGCTTTTCTCGAGCAGCAGCGAGACCCAGACTCGTACAA

CAAACACCTCTTCGTGCACATTGGGCATGCCAACCATTCTTACAGTGACCCATTGCTTGAATCA

GTGGACATTCGTCAGATTTATGACAAATTTCCTGAAAAGAAAGGTGGCTTAAAGGAACTGTTTG

GAAAGGGCCCTCAAAATGCCTTCTTCCTCGTAAAATTCTGGGCTGATTTAAACTGCAATATTCA

AGATGATGGTGGGGCTTTTTATGGTGTAACCAGTCAGTACGAGAGTTCTGAAAATATGACAGTC

ACCTGTTCCACCAAAGTTTGCTCCTTTGGGAAGCAAGTAGTAGAAAAAGTAGAGACGGAGTATG

CAAGGTTTGAGAATGGCCGATTTGTATACCGAATAAACCGCTCCCCAATGTGTGAATATATGAT

CAACTTCATCCACAAGCTCAAACACTTACCAGAGAAATATATGATGAACAGTGTTTTGGAAAAC

TTCACAATTTTATTGGTGGTAACAAACAGGGATACACAAGAAACTCTACTCTGCATGGCCTGTG

TGTTTGAAGTTTCAAATAGTGAACACGGAGCACAACATCATATTTACAGGCTTGTAAAGGACTG

A

SEQ ID NO: 50. TEAD1_HUMAN protein (426 amino acids)
MEPSSWSGSESPAENMERMSDSADKPIDNDAEGVWSPDIEQSFQEALAIYPPCGRRKIILSDEG

KMYGRNELIARYTKLRTGKTRTRKQVSSHIQVLARRKSRDFHSKLKDQTAKDKALQHMAAMSSA

QIVSATAIHNKLGLPGIPRPTFPGAPGFWPGMIQTGQPGSSQDVKPFVQQAYPIQPAVTAPIPG

FEPASAPAPSVPAWQGRSIGTTKLRLVEFSAFLEQQRDPDSYNKHLFVHIGHANHSYSDPLLES

VDIRQIYDKFPEKKGGLKELFGKGPQNAFFLVKFWADLNCNIQDDAGAFYGVTSQYESSENMTV

TCSTKVCSFGKQVVEKVETEYARFENGRFVYRINRSPMCEYMINFIHKLKHLPEKYMMNSVLEN

FTILLVVTNRDTQETLLCMACVFEVSNSEHGAQHHIYRLVKD

SEQ ID NO: 51. Large BiT (LgBiT) mRNA (477 nucleotides)
ATGGTCTTCACACTCGAAGATTTCGTTGGGGACTGGGAACAGACAGCCGCCTACAACCTGGACC

AAGTCCTTGAACAGGGAGGTGTGTCCAGTTTGCTGCAGAATCTCGCCGTGTCCGTAACTCCGAT

CCAAAGGATTGTCCGGAGCGGTGAAAATGCCCTGAAGATCGACATCCATGTCATCATCCCGTAT

GAAGGTCTGAGCGCCGACCAAATGGCCCAGATCGAAGAGGTGTTTAAGGTGGTGTACCCTGTGG

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ATGATCATCACTTTAAGGTGATCCTGCCCTATGGCACACTGGTAATCGACGGGGTTACGCCGAA

CATGCTGAACTATTTCGGACGGCCGTATGAAGGCATCGCCGTGTTCGACGGCAAAAAGATCACT

GTAACAGGGACCCTGTGGAACGGCAACAAAATTATCGACGAGCGCCTGATCACCCCCGACGGCT

CCATGCTGTTCCGAGTAACCATCAACAGT

SEQ ID NO: 52. Large BiT (LgBiT) protein (159 amino acids)
MVFTLEDFVGDWEQTAAYNLDQVLEQGGVSSLLQNLAVSVTPIQRIVRSGENALKIDIHVIIPY

EGLSADQMAQIEEVFKVVYPVDDHHFKVILPYGTLVIDGVTPNMLNYFGRPYSGIAVFDGKKIT

VTGTLWNGNKIIDERLITPDGSMLFRVTINS

SEQ ID NO: 53. Small BiT (SmBiT) mRNA (36 nucleotides)
ATGGTGACCGGCTACCGGCTGTTCGAGGAGATTCTC

SEQ ID NO: 54. Small BiT (SmBiT) protein (11 amino acids)
MVTGYRLFEIL

SEQ ID NO: 55. pcDNA3.1/hygro(+)-Flag vector (5,490 nucleotides)
GACGGATCGGGAGATCTCCCGATCCCCTATGGTGCACTCTCAGTACAATCTGCTCTGATGCCGC

ATAGTTAAGCCAGTATCTGCTCCCTGCTTGTGTGTTGGAGGTCGCTGAGTAGTGCGCGAGCAAA

ATTTAAGCTACACAAGGCAAGGCTTGACCGACAATTGCATGAAGAATCTGCTTAGGGTTAGGCG

TTTTGCGCTGCTTCGCGATGTACGGGCCAGATATACGCGTTGACATTGATTATTGACTAGTTAT

TAATAGTAATGAATTACGGGGTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAAC

TTACGGTAAATGGCCCGCCTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGAC

GTATGTTCCCATAGTAACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACGG

TAAACTGCCCACTTGGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTCA

ATGACGGTAAATGGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTTG

GCAGTACATCTACGTATTAGTCATCGCTATTACCATGGTGATGCGGTTTTGGCAGTACATCAAT

GGGCGTGGATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGACGTCAATGGGA

GTTTGTTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCGTAACAACTCCGCCCCATTGAC

GCAAATGGGCGGTAGGCGTGTACGGTGGGAGGTCTATATAAGCAGAGCTCTCTGGCTAACTAGA

GAACCCACTGCTTACTGGCTTATCGAAATTAATACGACTCACTATAGGGAGACCCAAGCTGGCT

AGCGTTTAAACTTAAGCTTGGTACCATGGACTACAAAGACGATGACGGTGATTATAAAGATCAT

GACATCTACCTGATGTTTCTGGTACTGCCAGGATCCACTAGTCCAGTGTGGTGGAATTCTGCAG

ATATCCAGGACAGTGGCGGCCGCTCGAGTCTAGAGGGCCCGTTTAAACCCGCTGATCAGCCTCG

ACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCCTCCCCCGTGCCTTCCTTGACCCTGG

AAGGTGCCACTCCCACTGTCCTTTCCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAG

GTGTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAAT

AGCAGGCATGCTGGGGATGCGGTGGGCTCTATGGCTTCTGAGGCGGAAAGAACCAGCTGGGGCT

CTAGGGGGTATCCCCACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCG

CAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTCGCTTTCTTCCCTTCCTTT

CTCGCCACGTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGAT

TTAGTGCTTTACGGCACCTCGACCCCAAAAAACTTGATTAGGGTGATGGTTCACGTAGTGGGCC

ATCGCCCTGATAGACGGTTTTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTC

TTGTTCCAAACTGGAACAACACTCAACCCTATCTCGGTCTATTCTTTTGATTTATAAGGGATTT

TGCCGATTTCGGCCTATTGGTTAAAAAATGAGCTGATTTAACAAAAATTTAACGCGAATTAATT

CTGTGGAATGTGTGTCAGTTAGGGTGTGGAAAGTCCCCAGGCTCCCCAGCAGGCAGAAGTATGC

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CCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTTTTTTATTT

ATGCAGAGGCCGAGGCCGCCTCTGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGG

AGGCCTAGGCTTTTGCAAAAAGCTCCCGGGAGCTTGTATATCCATTTTCGGATCTGATCAAGAG

ACAGGATGAGGATCGTTTCGCATGATTGAACAAGATGGATTGCACGCAGGTTCTCCGGCCGCTT

GGGTGGAGAGGCTATTCGGCTATGACTGGGCAGAACAGACAATCGGCTGCTCTGATGCCGCCGT

GTTCCGGCTGTCAGCGCAGGGGCGCCCGGTTCTTTTTGTCAAGACCGACCTGTCCGGTGCCCTG

AATGAACTGCAGGACGAGGCAGCGCGGCTATCGTGGCTGGCCACGACGGGCGTTCCTTGCGCAG

CTGTGCTCGACGTTGTCACTGAAGCGGGAAGGGACTGGCTGCTATTGGGCGAAGTGCCGGGGCA

GGATCTCCTGTCATCTCACCTTGCTCCTGCCGAGAAAGTATCCATCATGGCTGATGCAATGCGG

CGGCTGCATACGCTTGATCCGGCTACCTGCCCATTCGACCACCAAGCGAAACATCGCATCGAGC

GAGCACGTACTCGGATGGAAGCCGGTCTTGTCGATCAGGATGATCTGGACGAAGAGCATCAGGG

GCTCGCGCCAGCCGAACTGTTCGCCAGGCTCAAGGCGCGCATGCCCGACGGCGAGGATCTCGTC

GTGACCCATGGCGATGCCTGCTTGCCGAATATCATGGTGGAAAATGGCCGCTTTTCTGGATTCA

TCGACTGTGGCCGGCTGGGTGTGGCGGACCGCTATCAGGACATAGCGTTGGCTACCCGTGATAT

TGCTGAAGAGCTTGGCGGCGAATGGGCTGACCGCTTCCTCGTGCTTTACGGTATCGCCGCTCCC

GATTCGCAGCGCATCGCCTTCTATCGCCTTCTTGACGAGTTCTTCTGAGCGGGACTCTGGGGTT

CGAAATGACCGACCAAGCGACGCCCAACCTGCCATCACGAGATTTCGATTCCACCGCCGCCTTC

TATGAAAGGTTGGGCTTCGGAATCGTTTTCCGGGACGCCGGCTGGATGATCCTCCAGCGCGGGG

ATCTCATGCTGGAGTTCTTCGCCCACCCCAACTTGTTTATTGCAGCTTATAATGGTTACAAATA

AAGCAATAGCATCACAAATTTCACAAATAAAGCATTTTTTTCACTGCATTCTAGTTGTGGTTTG

TCCAAACTCATCAATGTATCTTATCATGTCTGTATACCGTCGACCTCTAGCTAGAGCTTGGCGT

AATCATGGTCATAGCTGTTTCCTGTGTGAAATTGTTATCCGCTCACAATTCCACACAACATACG

AGCCGGAAGCATAAAGTGTAAAGCCTGGGGTGCCTAATGAGTGAGCTAACTCACATTAATTGCG

TTGCGCTCACTGCCCGCTTTCCAGTCGGGAAACCTGTCGTGCCAGCTGCATTAATGAATCGGCC

AACGCGCGGGGAGAGGCGGTTTGCGTATTGGGCGCTCTTCCGCTTCCTCGCTCACTGACTCGCT

GCGCTCGGTCGTTCGGCTGCGGCGAGCGGTATCAGCTCACTCAAAGGCGGTAATACGGTTATCC

ACAGAATCAGGGGATAACGCAGGAAAGAACATGTGAGCAAAAGGCCAGCAAAAGGCCAGGAACC

GTAAAAAGGCCGCGTTGCTGGCGTTTTTCCATAGGCTCCGCCCCCCTGACGAGCATCACAAAAA

TCGACGCTCAAGTCAGAGGTGGCGAAACCCGACAGGACTATAAAGATACCAGGCGTTTCCCCCT

GGAAGCTCCCTCGTGCGCTCTCCTGTTCCGACCCTGCCGCTTACCGGATACCTGTCCGCCTTTC

CGTTCGCTCCAAGCTGGGCTGTGTGCACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCC

GGTAACTATCGTCTTGAGTCCAACCCGGTAAGACACGACTTATCGCCACTGGCAGCAGCCACTG

GTAACAGGATTAGCAGAGCGAGGTATGTAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGCCTAA

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AAAAGAGTTGGTAGCTCTTGATCCGGCAAACAAACCACCGCTGGTAGCGGTTTTTTTGTTTGCA

AGCAGCAGATTACGCGCAGAAAAAAAGGATCTCAAGAAGATCCTTTGATCTTTTCTACGGGGTC

TGACGCTCAGTGGAACGAAAACTCACGTTAAGGGATTTTGGTCATGAGATTATCAAAAAGGATC

TTCACCTAGATCCTTTTAAATTAAAAATGAAGTTTTAAATCAATCTAAAGTATATATGAGTAAA

CTTGGTCTGACAGTTACCAATGCTTAATCAGTGAGGCACCTATCTCAGCGATCTGTCTATTTCG

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GGCCCCAGTGCTGCAATGATACCGCGAGACCCACGCTCACCGGCTCCAGATTTATCAGCAATAA

ACCAGCCAGCCGGAAGGGCCGAGCGCAGAAGTGGTCCTGCAACTTTATCCGCCTCCATCCAGTC

TATTAATTGTTGCCGGGAAGCTAGAGTAAGTAGTTCGCCAGTTAATAGTTTGCGCAACGTTGTT

GCCATTGCTACAGGCATCGTGGTGTCACGCTCGTCGTTTGGTATGGCTTCATTCAGCTCCGGTT

CCCAACGATCAAGGCGAGTTACATGATCCCCCATGTTGTGCAAAAAAGCGGTTAGCTCCTTCGG

TCCTCCGATCGTTGTCAGAAGTAAGTTGGCCGCAGTGTTATCACTCATGGTTATGGCAGCACTG

CATAATTCTCTTACTGTCATGCCATCCGTAAGATGCTTTTCTGTGACTGGTGAGTACTCAACCA

AGTCATTCTGAGAATAGTGTATGCGGCGACCGAGTTGCTCTTGCCCGGCGTCAATACGGGATAA

TACCGCGCCACATAGCAGAACTTTAAAAGTGCTCATCATTGGAAAACGTTCTTCGGGGCGAAAA

CTCTCAAGGATCTTACCGCTGTTGAGATCCAGTTCGATGTAACCCACTCGTGCACCCAACTGAT

CTTCAGCATCTTTTACTTTCACCAGCGTTTCTGGGTGAGCAAAAACAGGAAGGCAAAATGCCGC

AAAAAAGGGAATAAGGGCGACACGGAAATGTTGAATACTCATACTCTTCCTTTTTCAATATTAT

TGAAGCATTTATCAGGGTTATTGTCTCATGAGCGGATACATATTTGAATGTATTTAGAAAAATA

AACAAATAGGGGTTCCGCGCACATTTCCCCGAAAAGTGCCACCTGACGTC

SEQ ID NO: 56 pcDNA3.1/hygro(+)-Myc vector (5,455 nucleotides)
GACGGATCGGGAGATCTCCCGATCCCCTATGGTGCACTCTCAGTACAATCTGCTCTGATGCCGC

ATAGTTAAGCCAGTATCTGCTCCCTGCTTGTGTGTTGGAGGTCGCTGAGTAGTGCGCGAGCAAA

ATTTAAGCTACAACAAGGCAAGGCTTGACCGACAATTGCATGAAGAATCTGCTTAGGGTTAGGC

GTTTTGCGCTGCTTCGCGATGTACGGGCCAGATATACGCGTTGACATTGATTATTGACTAGTTA

TTAATAGTAATCAATTACGGGGTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAA

CTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGA

CGTATGTTCCCATAGTAACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTTACG

GTAAACTGCCCACTTGGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCCCTATTGACGTC

AATGACGGTAAATGGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTCCTACTT

GGCAGTACATCTACGTATTAGTCATCGCTATTACCATGGTGATGCGGTTTTGGCAGTACATCAA

TGGGCGTGGATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGACGTCAATGGG

AGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCGTAACAACTCCGCCCCATTGA

CGCAAATGGGCGGTAGGCGTGTACGGTGGGAGGTCTATATAAGCAGAGCTCTCTGGCTAACTAG

AGAACCCACTGCTTACTGGCTTATCGAAATTAATACGACTCACTATAGGGAGACCCAAGCTGGC

TAGCGTTTAAACTTAAGCTTGGTACCATGGAACAAAAACTCATCTCAGAAGAGGATCTGGGATC

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SEQ ID NO: 57. Intermolecular biosensor Nluc-YAP15 in pcDNA3.1/ hygro(+) vector (6,693 nucleotides)

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SEQ ID NO: 58. Intermolecular biosensor 14-3-3-Cluc in pcDNA3.1/ hygro(+) vector (6,621 nucleotides)

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TCCGGCAAACAAACCACCGCTGGTAGCGGTTTTTTTGTTTGCAAGCAGCAGATTACGCGCAGAA

AAAAAGGATCTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACGCTCAGTGGAACGAAAA

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AGCGCAGAAGTGGTCCTGCAACTTTATCCGCCTCCATCCAGTCTATTAATTGTTGCCGGGAAGC

TAGAGTAAGTAGTTCGCCAGTTAATAGTTTGCGCAACGTTGTTGCCATTGCTACAGGCATCGTG

GTGTCACGCTCGTCGTTTGGTATGGCTTCATTCAGCTCCGGTTCCCAACGATCAAGGCGAGTTA

CATGATCCCCCATGTTGTGCAAAAAAGCGGTTAGCTCCTTCGGTCCTCCGATCGTTGTCAGAAG

TAAGTTGGCCGCAGTGTTATCACTCATGGTTATGGCAGCACTGCATAATTCTCTTACTGTCATG

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TGTCTCATGAGCGGATACATATTTGAATGTATTTAGAAAAATAAACAAATAGGGGTTCCGCGCA

CATTTCCCCGAAAAGTGCCACCTGACGTC

SEQ ID NO: 59. NanoBiT Biosensor: LgBiT-YAP15 in pBiT 1.1 N vector (3,890 nucleotides)

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CGGCGACGGGCTCGCTGGGTCCTAGGCTCCATGGGGACCGTATACGTGGACAGGCTCTGGAGCA

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CCGGAGCGTCCGTTGGGCGACAAACACCAGGACGGGGCACAGGTACACTATCTTGTCACCCGGA

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CCCAGGTCCACTTCGCATATTAAGGTGACGCGTGTGGCCTCGAACACCGAGCGACCCTGCAGCG

ACCCGCTTAAAAGCTTGGCAATCCGGTACTGTTGGTAAAGCCACC**ATGGTCTTCACACTCGAAG**

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TGTGTCCAGTTTGCTGCAGAATCTCGCCGTGTCCGTAACTCCGATCCAAAGGATTGTCCGGAGC

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GATCCTGCCCTATGGCACACTGGTAATCGACGGGGTTACGCCGAACATGCTGAACTATTTCGGA

CGGCCGTATGAAGGCATCGCCGTGTTCGACGGCAAAAAGATCACTGTAACAGGGACCCTGTGGA

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TTTTGTGTGAATCGATAGTACTAACATACGCTCTCCATCAAAACAAAACGAAACAAAACAAACT

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SEQ ID NO: 60. NanoBiT Biosensor: 14-3-3-LgBiT in pBiT2.1-C vector (4,131 nucleotides)

GGCCTAACTGGCCGGTACCTGAGTCTAAATGAGTCTTCGGACCTCGCGGGGGCCGCTTAAGCGG

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CCGCCCTCCGTGGAGGCGGGGGTTTGGTCGGCGGGTGGTAACTGGCGGGCCGCTGACTCGGGCG

GGTCGCGCGCCCCAGAGTGTGACCTTTTCGGTCTGCTCGCAGACCCCCGGGCGGCGCCGCCGCG

GCGGCGACGGGCTCGCTGGGTCCTAGGCTCCATGGGGACCGTATACGTGGACAGGCTCTGGAGC

ATCCGCACGACTGCGGTGATATTACCGGAGACCTTCTGCGGGACGAGCCGGGTCACGCGGCTGA

CGCGGAGCGTCCGTTGGGCGACAAACACCAGGACGGGGCACAGGTACACTATCTTGTCACCCGG

AGGCGCGAGGGACTGCAGGAGCTTCAGGGAGTGGCGCAGCTGCTTCATCCCCGTGGCCCGTTGC

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GAGCTGATCCAGAAGGCCAAGCTGGCCGAGCAGGCCGAGCGCTACGACGACATGGCCACCTGCA

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GCCGCACTTATGACTGTCTTCTTTATCATGCAACTCGTAGGACAGGTGCCGGCAGCGCTCTTCC

GCTTCCTCGCTGACTGACTCGCTGCGCTCGGTCGTTCGGCTGCGGCGAGCGGTATCAGCTCACT

CAAAGGCGGTAATACGGTTATCCACAGAATCAGGGGATAACGCAGGAAAGAACATGTGAGCAAA

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CCCCCTGACGAGCATCACAAAAATCGACGCTCAAGTCAGAGGTGGCGAAACCCGACAGGACTAT

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TAGTACTAACATACGCTCTCCATCAAAACAAAACGAAACAAAACAAACTAGCAAAATAGGCTGT

CCCCAGTGCAAGTGCAGGTGCCAGAACATTTCTCT

SEQ ID NO: 61. NanoBiT Biosensor: LgBiT-YAP15 in pET16b vector (6,291 nucleotides)

TTCTTGAAGACGAAAGGGCCTCGTGATACGCCTATTTTTATAGGTTAATGTCATGATAATAATG

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TTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTGCGGCA

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CGTGTTGACGCCGGGCAAGAGCAACTCGGTCGCCGCATACACTATTCTCAGAATGACTTGGTTG

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TCCGATCCAAAGGATTGTCCGGAGCGGTGAAAATGCCCTGAAGATCGACATCCATGTCATCATC

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ATGCCTACAGCATCCAGGGTGACGGTGCTGAGGATGACGATGAGCGCATTGTTAGATTTCATAC

ACGGTGCCTGACTGCGTTAGCAATTTAACTGTGATAAACTACCGCATTAAAGCTTATCGATGAT

AAGCTGTCAAACATGAGAA

SEQ ID NO: 62. NanoBiT Biosensor: SmBiT in pET16b vector
(6,531 nucleotides)

TTCTTGAAGACGAAAGGGCCTCGTGATACGCCTATTTTTATAGGTTAATGTCATGATAATAATG

GTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTT

TCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATA

TTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTGCGGCA

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SEQ ID NO: 63. YAP-TEAD NanoBiT biosensor construct 1: LgBiT-YAP50-171-Flag in pcDNA3.1-hygro vector (6,297 nucleotides)
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SEQ ID NO: 64. YAP-TEAD NanoBiT biosensor construct 2: Flag-YAP50-171-LgBiT in pcDNA3.1-hygro vector (6,270 nucieotides)

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SEQ ID NO: 65. YAP-TEAD NanoBiT biosensor construct 3: SmBiT-YAP50-171-Flag in pcDNA3.1-hygro vector (5,856 nucleotides)

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SEQ ID NO: 66. YAP-TEAD NanoBiT biosensor construct 4: Flag-YAP50-171-SmBiT in pcDNA3.1-hygro vector (5,829 nucleotides)
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SEQ ID NO: 67. YAP-TEAD NanoBiT biosensor construct 5: LgBiT-TEAD1-194-411-Myc in pcDNA3.1-hygro vector (6,592 nucleotides)

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SEQ ID NO: 68. YAP-TEAD NanoBiT biosensor construct 6: Myc-TEAD1-194-411-LgBiT in pcDNA3.1-hygro vector (6,559 nucleotides)

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SEQ ID NO: 69. YAP-TEAD NanoBiT biosensor construct 7: SmBiT-TEAD1-194-411-Myc in pcDNA3.1-hygro vector (6,151 nucleotides)
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SEQ ID NO: 70. YAP-TEAD NanoBiT biosensor construct 8: Myc-TEAD1-194-411-SmBiT in pcDNA3.1-hygro vector (6,118 nucleotides)

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EQUIVALENTS

While the invention has been described with respect to illustrative embodiments thereof, it will be understood that various changes may be made to the embodiments without departing from the scope of the invention. Accordingly, the described embodiments are to be considered merely exemplary and the invention is not to be limited thereby.

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SEQUENCE LISTING

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35 40 45

Pro Ala Gly His Gln Ile Val His Val Arg Gly Asp Ser Glu Thr Asp
50 55 60

Leu Glu Ala Leu Phe Asn Ala Val Met Asn Pro Lys Thr Ala Asn Val
65 70 75 80

Pro Gln Thr Val Pro Met Arg Leu Arg Lys Leu Pro Asp Ser Phe Phe
85 90 95

Lys Pro Pro Glu Pro Lys Ser His Ser Arg Gln Ala Ser Thr Asp Ala
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Gly Thr Ala Gly Ala Leu Thr Pro Gln His Val Arg Ala His Ser Ser
115 120 125

Pro Ala Ser Leu Gln Leu Gly Ala Val Ser Pro Gly Thr Leu Thr Pro
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Thr Gly Val Val Ser Gly Pro Ala Ala Thr Pro Thr Ala Gln His Leu
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Arg Gln Ser Ser Phe Glu Ile Pro Asp Asp Val Pro Leu Pro Ala Gly
165 170 175

Trp Glu Met Ala Lys Thr Ser Ser Gly Gln Arg Tyr Phe Leu Asn His
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Ile Asp Gln Thr Thr Thr Trp Gln Asp Pro Arg Lys Ala Met Leu Ser
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Gln Met Asn Val Thr Ala Pro Thr Ser Pro Pro Val Gln Gln Asn Met
210 215 220

Met Asn Ser Ala Ser Gly Pro Leu Pro Asp Gly Trp Glu Gln Ala Met
225 230 235 240

Thr Gln Asp Gly Glu Ile Tyr Tyr Ile Asn His Lys Asn Lys Thr Thr
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Ser Trp Leu Asp Pro Arg Leu Asp Pro Arg Phe Ala Met Asn Gln Arg
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Lys Gln Gln Glu Leu Leu Arg Gln Ala Met Arg Asn Ile Asn Pro Ser
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Lys Asn Val Val Gly Gly Arg Arg Ser Ala Trp Arg Val Ile Ser Ser
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Ile Glu Gln Lys Thr Asp Thr Ser Asp Lys Lys Leu Gln Leu Ile Lys
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Asp Tyr Arg Glu Lys Val Glu Ser Glu Leu Arg Ser Ile Cys Thr Thr
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Val Leu Glu Leu Leu Asp Lys Tyr Leu Ile Ala Asn Ala Thr Asn Pro
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Glu Ser Lys Val Phe Tyr Leu Lys Met Lys Gly Asp Tyr Phe Arg Tyr
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Leu Ala Glu Val Ala Cys Gly Asp Asp Arg Lys Gln Thr Ile Asp Asn
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Ser Gln Gly Ala Tyr Gln Glu Ala Phe Asp Ile Ser Lys Lys Glu Met
145                 150                 155                 160

Gln Pro Thr His Pro Ile Arg Leu Gly Leu Ala Leu Asn Phe Ser Val
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Phe Tyr Tyr Glu Ile Leu Asn Asn Pro Glu Leu Ala Cys Thr Leu Ala
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Lys Thr Ala Phe Asp Glu Ala Ile Ala Glu Leu Asp Thr Leu Asn Glu
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Val Asp Ile Thr Tyr Ala Glu Tyr Phe Glu Met Ser Val Arg Leu Ala
    50                  55                  60

Glu Ala Met Lys Arg Tyr Gly Leu Asn Thr Asn His Arg Ile Val Val
65                  70                  75                  80

Cys Ser Glu Asn Ser Leu Gln Phe Phe Met Pro Val Leu Gly Ala Leu
                85                  90                  95

Phe Ile Gly Val Ala Val Ala Pro Ala Asn Asp Ile Tyr Asn Glu Arg
            100                 105                 110

Glu Leu Leu Asn Ser Met Gly Ile Ser Gln Pro Thr Val Val Phe Val
        115                 120                 125

Ser Lys Lys Gly Leu Gln Lys Ile Leu Asn Val Gln Lys Lys Leu Pro
    130                 135                 140

Ile Ile Gln Lys Ile Ile Ile Met Asp Ser Lys Thr Asp Tyr Gln Gly
145                 150                 155                 160

Phe Gln Ser Met Tyr Thr Phe Val Thr Ser His Leu Pro Pro Gly Phe
                165                 170                 175

Asn Glu Tyr Asp Phe Val Pro Glu Ser Phe Asp Arg Asp Lys Thr Ile
            180                 185                 190

Ala Leu Ile Met Asn Ser Ser Gly Ser Thr Gly Leu Pro Lys Gly Val
        195                 200                 205

Ala Leu Pro His Arg Thr Ala Cys Val Arg Phe Ser His Ala Arg Asp
    210                 215                 220

Pro Ile Phe Gly Asn Gln Ile Ile Pro Asp Thr Ala Ile Leu Ser Val
225                 230                 235                 240

Val Pro Phe His His Gly Phe Gly Met Phe Thr Thr Leu Gly Tyr Leu
                245                 250                 255

Ile Cys Gly Phe Arg Val Val Leu Met Tyr Arg Phe Glu Glu Glu Leu
            260                 265                 270

Phe Leu Arg Ser Leu Gln Asp Tyr Lys Ile Gln Ser Ala Leu Leu Val
        275                 280                 285

Pro Thr Leu Phe Ser Phe Phe Ala Lys Ser Thr Leu Ile Asp Lys Tyr
    290                 295                 300

Asp Leu Ser Asn Leu His Glu Ile Ala Ser Gly Gly Ala Pro Leu Ser
305                 310                 315                 320

Lys Glu Val Gly Glu Ala Val Ala Lys Arg Phe His Leu Pro Gly Ile
                325                 330                 335

Arg Gln Gly Tyr Gly Leu Thr Glu Thr Thr Ser Ala Ile Leu Ile Thr
            340                 345                 350

Pro Glu Gly Asp Asp Lys Pro Gly Ala Val Gly Lys Val Val Pro Phe
        355                 360                 365

Phe Glu Ala Lys Val Val Asp Leu Asp Thr Gly Lys Thr Leu Gly Val
    370                 375                 380

Asn Gln Arg Gly Glu Leu Cys Val Arg Gly Pro Met Ile Met Ser Gly
385                 390                 395                 400
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Tyr Val Asn Asn Pro Glu Ala Thr Asn Ala Leu Ile Asp Lys Asp Gly
                405                 410                 415

Trp Leu His Ser Gly Asp Ile Ala Tyr Trp Asp Glu Asp Glu His Phe
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Phe Ile Val Asp Arg Leu Lys Ser Leu Ile Lys Tyr Lys Gly Tyr Gln
        435                 440                 445

Val Ala Pro Ala Glu Leu Glu Ser Ile Leu Leu Gln His Pro Asn Ile
    450                 455                 460

Phe Asp Ala Gly Val Ala Gly Leu Pro Asp Asp Ala Gly Glu Leu
465                 470                 475                 480

Pro Ala Ala Val Val Val Leu Glu His Gly Lys Thr Met Thr Glu Lys
                485                 490                 495

Glu Ile Val Asp Tyr Val Ala Ser Gln Val Thr Thr Ala Lys Lys Leu
            500                 505                 510

Arg Gly Gly Val Val Phe Val Asp Glu Val Pro Lys Gly Leu Thr Gly
        515                 520                 525

Lys Leu Asp Ala Arg Lys Ile Arg Glu Ile Leu Ile Lys Ala Lys Lys
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Gly Gly Lys Ile Ala Val
545                 550


<210> SEQ ID NO 7
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

Pro Gln His Val Arg His Ala Ser Ser Pro Ala Ser Leu Gln Leu
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<210> SEQ ID NO 8
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 8

Pro Gln His Val Arg His Ala Ala Ser Pro Ala Ser Leu Gln Leu
1               5                   10                  15


<210> SEQ ID NO 9
<211> LENGTH: 5597
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Vector

<400> SEQUENCE: 9

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cgagcaaaat ttaagctaca acaaggcaag gcttgaccga caattgcatg aagaatctgc     180

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<212> TYPE: DNA
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<220> FEATURE:
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<210> SEQ ID NO 12
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<210> SEQ ID NO 13
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<400> SEQUENCE: 16

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<220> FEATURE:
<223> OTHER INFORMATION: Primer

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<400> SEQUENCE: 18

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<220> FEATURE:
<223> OTHER INFORMATION: Primer

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<210> SEQ ID NO 20
<211> LENGTH: 55
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 20

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<210> SEQ ID NO 21
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<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 21

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<210> SEQ ID NO 22
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<212> TYPE: DNA
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<400> SEQUENCE: 22

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<210> SEQ ID NO 23
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 24

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<210> SEQ ID NO 25
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 25

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<210> SEQ ID NO 26
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 26

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<210> SEQ ID NO 28
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 28

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<210> SEQ ID NO 29
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 29

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<210> SEQ ID NO 30
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 30

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<210> SEQ ID NO 31
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 31

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<210> SEQ ID NO 32
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 32

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<210> SEQ ID NO 33
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 34

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<210> SEQ ID NO 35
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 35

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<210> SEQ ID NO 36
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 36

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<210> SEQ ID NO 37
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 37

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<210> SEQ ID NO 38
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 38

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<210> SEQ ID NO 39
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<210> SEQ ID NO 40
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 40

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<210> SEQ ID NO 41
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 41

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<220> FEATURE:
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<400> SEQUENCE: 42

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<210> SEQ ID NO 43
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

<223> OTHER INFORMATION: Primer

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 45

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caaacacaca ggc 73

<210> SEQ ID NO 46
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 46

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<210> SEQ ID NO 47
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 47

acctgacgac cctccacctc cgctcccgcc accaccgctc gagccatttg aaacttcaaa 60

cacacaggc 69

<210> SEQ ID NO 48
<211> LENGTH: 73
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 48

gggagttccg gtggtggcgg gagcggaggt ggaggctcga gcggtgagcc tgcatcggcc 60

ccagctccct cag 73

<210> SEQ ID NO 49
<211> LENGTH: 1281

<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 49

```
attgagccca gcagctggag cggcagtgag agccctgccg aaaacatgga aaggatgagt     60

gactctgcag ataagccaat tgacaatgat gcagaagggg tctggagccc cgacatcgag    120

caaagctttc aggaggccct ggctatctat ccaccatgtg ggaggaggaa aatcatctta    180

tcagacgaag gcaaaatgta tggtaggaat gaattgatag ccagatacat caaactcagg    240

acaggcaaga cgaggaccag aaaacaggtg tctagtcaca ttcaggttct tgccagaagg    300

aaatctcgtg attttcattc caagctaaag gatcagactg caaaggataa ggccctgcag    360

cacatggcgg ccatgtcctc agcccagatc gtctcggcca ctgccattca taacaagctg    420

gggctgcctg ggattccacg cccgaccttc ccaggggcgc cggggttctg gccgggaatg    480

attcaaacag ggcagccagg atcctcacaa gacgtcaagc cttttgtgca gcaggcctac    540

cccatccagc cagcggtcac agccccccatt ccagggtttg agcctgcatc ggccccagct    600

ccctcagtcc ctgcctggca aggtcgctcc attggcacaa ccaagcttcg cctggtggaa    660

ttttcagctt ttctcgagca gcagcgagac ccagactcgt acaacaaaca cctcttcgtg    720

cacattgggc atgccaacca ttcttacagt gacccattgc ttgaatcagt ggacattcgt    780

cagatttatg acaaatttcc tgaaaagaaa ggtggcttaa aggaactgtt tggaaagggc    840

cctcaaaatg ccttcttcct cgtaaaattc tgggctgatt taaactgcaa tattcaagat    900

gatgctgggg ctttttatgg tgtaaccagt cagtacgaga gttctgaaaa tatgacagtc    960

acctgttcca ccaaagtttg ctcctttggg aagcaagtag tagaaaaagt agagacggag   1020

tatgcaaggt ttgagaatgg ccgatttgta taccgaataa accgctcccc aatgtgtgaa   1080

tatatgatca acttcatcca caagctcaaa cacttaccag agaaatatat gatgaacagt   1140

gttttggaaa acttcacaat tttattggtg gtaacaaaca gggatacaca agaaactcta   1200

ctctgcatgg cctgtgtgtt tgaagtttca aatagtgaac acggagcaca acatcatatt   1260

tacaggcttg taaaggactg a                                              1281
```

<210> SEQ ID NO 50
<211> LENGTH: 426
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 50

```
Met Glu Pro Ser Ser Trp Ser Gly Ser Glu Ser Pro Ala Glu Asn Met
1               5                   10                  15

Glu Arg Met Ser Asp Ser Ala Asp Lys Pro Ile Asp Asn Asp Ala Glu
            20                  25                  30

Gly Val Trp Ser Pro Asp Ile Glu Gln Ser Phe Gln Glu Ala Leu Ala
        35                  40                  45

Ile Tyr Pro Pro Cys Gly Arg Arg Lys Ile Ile Leu Ser Asp Glu Gly
    50                  55                  60

Lys Met Tyr Gly Arg Asn Glu Leu Ile Ala Arg Tyr Ile Lys Leu Arg
65                  70                  75                  80

Thr Gly Lys Thr Arg Thr Arg Lys Gln Val Ser Ser His Ile Gln Val
                85                  90                  95

Leu Ala Arg Arg Lys Ser Arg Asp Phe His Ser Lys Leu Lys Asp Gln
            100                 105                 110
```

```
Thr Ala Lys Asp Lys Ala Leu Gln His Met Ala Ala Met Ser Ser Ala
        115                 120                 125

Gln Ile Val Ser Ala Thr Ala Ile His Asn Lys Leu Gly Leu Pro Gly
    130                 135                 140

Ile Pro Arg Pro Thr Phe Pro Gly Ala Pro Gly Phe Trp Pro Gly Met
145                 150                 155                 160

Ile Gln Thr Gly Gln Pro Gly Ser Ser Gln Asp Val Lys Pro Phe Val
                165                 170                 175

Gln Gln Ala Tyr Pro Ile Gln Pro Ala Val Thr Ala Pro Ile Pro Gly
            180                 185                 190

Phe Glu Pro Ala Ser Ala Pro Ala Pro Ser Val Pro Ala Trp Gln Gly
        195                 200                 205

Arg Ser Ile Gly Thr Thr Lys Leu Arg Leu Val Glu Phe Ser Ala Phe
    210                 215                 220

Leu Glu Gln Gln Arg Asp Pro Asp Ser Tyr Asn Lys His Leu Phe Val
225                 230                 235                 240

His Ile Gly His Ala Asn His Ser Tyr Ser Asp Pro Leu Leu Glu Ser
                245                 250                 255

Val Asp Ile Arg Gln Ile Tyr Asp Lys Phe Pro Glu Lys Lys Gly Gly
            260                 265                 270

Leu Lys Glu Leu Phe Gly Lys Gly Pro Gln Asn Ala Phe Phe Leu Val
        275                 280                 285

Lys Phe Trp Ala Asp Leu Asn Cys Asn Ile Gln Asp Asp Ala Gly Ala
    290                 295                 300

Phe Tyr Gly Val Thr Ser Gln Tyr Glu Ser Ser Glu Asn Met Thr Val
305                 310                 315                 320

Thr Cys Ser Thr Lys Val Cys Ser Phe Gly Lys Gln Val Val Glu Lys
                325                 330                 335

Val Glu Thr Glu Tyr Ala Arg Phe Glu Asn Gly Arg Phe Val Tyr Arg
            340                 345                 350

Ile Asn Arg Ser Pro Met Cys Glu Tyr Met Ile Asn Phe Ile His Lys
        355                 360                 365

Leu Lys His Leu Pro Glu Lys Tyr Met Met Asn Ser Val Leu Glu Asn
    370                 375                 380

Phe Thr Ile Leu Leu Val Val Thr Asn Arg Asp Thr Gln Glu Thr Leu
385                 390                 395                 400

Leu Cys Met Ala Cys Val Phe Glu Val Ser Asn Ser Glu His Gly Ala
                405                 410                 415

Gln His His Ile Tyr Arg Leu Val Lys Asp
            420                 425
```

<210> SEQ ID NO 51
<211> LENGTH: 477
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 51

```
atggtcttca cactcgaaga tttcgttggg gactgggaac agacagccgc ctacaacctg     60

gaccaagtcc ttgaacaggg aggtgtgtcc agtttgctgc agaatctcgc cgtgtccgta    120

actccgatcc aaaggattgt ccggagcggt gaaaatgccc tgaagatcga catccatgtc    180

atcatcccgt atgaaggtct gagcgccgac caaatggccc agatcgaaga ggtgtttaag    240
```

-continued

```
gtggtgtacc ctgtggatga tcatcacttt aaggtgatcc tgccctatgg cacactggta    300

atcgacgggg ttacgccgaa catgctgaac tatttcggac ggccgtatga aggcatcgcc    360

gtgttcgacg gcaaaaagat cactgtaaca gggaccctgt ggaacggcaa caaaattatc    420

gacgagcgcc tgatcacccc cgacggctcc atgctgttcc gagtaaccat caacagt       477
```

<210> SEQ ID NO 52
<211> LENGTH: 159
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 52

```
Met Val Phe Thr Leu Glu Asp Phe Val Gly Asp Trp Glu Gln Thr Ala
1               5                   10                  15

Ala Tyr Asn Leu Asp Gln Val Leu Glu Gln Gly Gly Val Ser Ser Leu
            20                  25                  30

Leu Gln Asn Leu Ala Val Ser Val Thr Pro Ile Gln Arg Ile Val Arg
        35                  40                  45

Ser Gly Glu Asn Ala Leu Lys Ile Asp Ile His Val Ile Ile Pro Tyr
    50                  55                  60

Glu Gly Leu Ser Ala Asp Gln Met Ala Gln Ile Glu Glu Val Phe Lys
65                  70                  75                  80

Val Val Tyr Pro Val Asp Asp His His Phe Lys Val Ile Leu Pro Tyr
                85                  90                  95

Gly Thr Leu Val Ile Asp Gly Val Thr Pro Asn Met Leu Asn Tyr Phe
            100                 105                 110

Gly Arg Pro Tyr Glu Gly Ile Ala Val Phe Asp Gly Lys Lys Ile Thr
        115                 120                 125

Val Thr Gly Thr Leu Trp Asn Gly Asn Lys Ile Ile Asp Glu Arg Leu
    130                 135                 140

Ile Thr Pro Asp Gly Ser Met Leu Phe Arg Val Thr Ile Asn Ser
145                 150                 155
```

<210> SEQ ID NO 53
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 53

```
atggtgaccg gctaccggct gttcgaggag attctc                                36
```

<210> SEQ ID NO 54
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthesized

<400> SEQUENCE: 54

```
Met Val Thr Gly Tyr Arg Leu Phe Glu Ile Leu
1               5                   10
```

<210> SEQ ID NO 55
<211> LENGTH: 5490
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

<223> OTHER INFORMATION: Vector

<400> SEQUENCE: 55

```
gacggatcgg gagatctccc gatcccctat ggtgcactct cagtacaatc tgctctgatg     60
ccgcatagtt aagccagtat ctgctccctg cttgtgtgtt ggaggtcgct gagtagtgcg    120
cgagcaaaat ttaagctaca caaggcaagg cttgaccgac aattgcatga agaatctgct    180
tagggttagg cgttttgcgc tgcttcgcga tgtacgggcc agatatacgc gttgacattg    240
attattgact agttattaat agtaatcaat tacggggtca ttagttcata gcccatatat    300
ggagttccgc gttacataac ttacggtaaa tggcccgcct ggctgaccgc ccaacgaccc    360
ccgcccattg acgtcaataa tgacgtatgt tcccatagta acgccaatag ggactttcca    420
ttgacgtcaa tgggtggagt atttacggta aactgcccac ttggcagtac atcaagtgta    480
tcatatgcca agtacgcccc ctattgacgt caatgacggt aaatggcccg cctggcatta    540
tgcccagtac atgaccttat gggactttcc tacttggcag tacatctacg tattagtcat    600
cgctattacc atggtgatgc ggttttggca gtacatcaat gggcgtggat agcggtttga    660
ctcacgggga tttccaagtc tccaccccat tgacgtcaat gggagtttgt tttggcacca    720
aaatcaacgg gactttccaa aatgtcgtaa caactccgcc ccattgacgc aaatgggcgg    780
taggcgtgta cggtgggagg tctatataag cagagctctc tggctaacta gagaacccac    840
tgcttactgg cttatcgaaa ttaatacgac tcactatagg gagacccaag ctggctagcg    900
tttaaactta agcttggtac catggactac aaagacgatg acggtgatta taaagatcat    960
gacatctacc tgatgtttct ggtactgcca ggatccacta gtccagtgtg gtggaattct   1020
gcagatatcc agcacagtgg cggccgctcg agtctagagg gcccgtttaa acccgctgat   1080
cagcctcgac tgtgccttct agttgccagc catctgttgt ttgcccctcc cccgtgcctt   1140
ccttgaccct ggaaggtgcc actcccactg tcctttccta ataaaatgag gaaattgcat   1200
cgcattgtct gagtaggtgt cattctattc tggggggtgg ggtggggcag gacagcaagg   1260
gggaggattg ggaagacaat agcaggcatg ctggggatgc ggtgggctct atggcttctg   1320
aggcggaaag aaccagctgg ggctctaggg ggtatcccca cgcgccctgt agcggcgcat   1380
taagcgcggc gggtgtggtg gttacgcgca gcgtgaccgc tacacttgcc agcgccctag   1440
cgcccgctcc tttcgctttc ttcccttcct ttctcgccac gttcgccggc tttccccgtc   1500
aagctctaaa tcgggggctc cctttagggt tccgatttag tgctttacgg cacctcgacc   1560
ccaaaaaact tgattagggt gatggttcac gtagtgggcc atcgccctga tagacggttt   1620
ttcgcccttt gacgttggag tccacgttct ttaatagtgg actcttgttc caaactggaa   1680
caacactcaa ccctatctcg gtctattctt ttgatttata agggattttg ccgatttcgg   1740
cctattggtt aaaaaatgag ctgatttaac aaaaatttaa cgcgaattaa ttctgtggaa   1800
tgtgtgtcag ttagggtgtg gaaagtcccc aggctcccca gcaggcagaa gtatgcaaag   1860
catgcatctc aattagtcag caaccaggtg tggaaagtcc ccaggctccc cagcaggcag   1920
aagtatgcaa agcatgcatc tcaattagtc agcaaccata gtcccgcccc taactccgcc   1980
catcccgccc ctaactccgc ccagttccgc ccattctccg ccccatggct gactaatttt   2040
ttttatttat gcagaggccg aggccgcctc tgcctctgag ctattccaga agtagtgagg   2100
aggctttttt ggaggcctag gcttttgcaa aaagctcccg ggagcttgta tatccatttt   2160
cggatctgat caagagacag gatgaggatc gtttcgcatg attgaacaag atggattgca   2220
cgcaggttct ccggccgctt gggtggagag gctattcggc tatgactggg cacaacagac   2280
```

```
aatcggctgc tctgatgccg ccgtgttccg gctgtcagcg caggggcgcc cggttctttt   2340
tgtcaagacc gacctgtccg gtgccctgaa tgaactgcag gacgaggcag cgcggctatc   2400
gtggctggcc acgacgggcg ttccttgcgc agctgtgctc gacgttgtca ctgaagcggg   2460
aagggactgg ctgctattgg gcgaagtgcc ggggcaggat ctcctgtcat ctcaccttgc   2520
tcctgccgag aaagtatcca tcatggctga tgcaatgcgg cggctgcata cgcttgatcc   2580
ggctacctgc ccattcgacc accaagcgaa acatcgcatc gagcgagcac gtactcggat   2640
ggaagccggt cttgtcgatc aggatgatct ggacgaagag catcaggggc tcgcgccagc   2700
cgaactgttc gccaggctca aggcgcgcat gcccgacggc gaggatctcg tcgtgaccca   2760
tggcgatgcc tgcttgccga atatcatggt ggaaaatggc cgcttttctg gattcatcga   2820
ctgtggccgg ctgggtgtgg cggaccgcta tcaggacata gcgttggcta cccgtgatat   2880
tgctgaagag cttggcggcg aatgggctga ccgcttcctc gtgctttacg gtatcgccgc   2940
tcccgattcg cagcgcatcg ccttctatcg ccttcttgac gagttcttct gagcgggact   3000
ctggggttcg aaatgaccga ccaagcgacg cccaacctgc catcacgaga tttcgattcc   3060
accgccgcct tctatgaaag gttgggcttc ggaatcgttt tccgggacgc cggctggatg   3120
atcctccagc gcggggatct catgctggag ttcttcgccc accccaactt gtttattgca   3180
gcttataatg gttacaaata aagcaatagc atcacaaatt tcacaaataa agcatttttt   3240
tcactgcatt ctagttgtgg tttgtccaaa ctcatcaatg tatcttatca tgtctgtata   3300
ccgtcgacct ctagctagag cttggcgtaa tcatggtcat agctgtttcc tgtgtgaaat   3360
tgttatccgc tcacaattcc acacaacata cgagccggaa gcataaagtg taaagcctgg   3420
ggtgcctaat gagtgagcta actcacatta attgcgttgc gctcactgcc cgctttccag   3480
tcgggaaacc tgtcgtgcca gctgcattaa tgaatcggcc aacgcgcggg gagaggcggt   3540
ttgcgtattg ggcgctcttc cgcttcctcg ctcactgact cgctgcgctc ggtcgttcgg   3600
ctgcggcgag cggtatcagc tcactcaaag gcggtaatac ggttatccac agaatcaggg   3660
gataacgcag gaaagaacat gtgagcaaaa ggccagcaaa aggccaggaa ccgtaaaaag   3720
gccgcgttgc tggcgttttt ccataggctc cgcccccctg acgagcatca caaaaatcga   3780
cgctcaagtc agaggtggcg aaacccgaca ggactataaa gataccaggc gtttccccct   3840
ggaagctccc tcgtgcgctc tcctgttccg accctgccgc ttaccggata cctgtccgcc   3900
tttctccctt cgggaagcgt ggcgctttct catagctcac gctgtaggta tctcagttcg   3960
gtgtaggtcg ttcgctccaa gctgggctgt gtgcacgaac cccccgttca gcccgaccgc   4020
tgcgccttat ccggtaacta tcgtcttgag tccaacccgg taagacacga cttatcgcca   4080
ctggcagcag ccactggtaa caggattagc agagcgaggt atgtaggcgg tgctacagag   4140
ttcttgaagt ggtggcctaa ctacggctac actagaagaa cagtatttgg tatctgcgct   4200
ctgctgaagc cagttacctt cggaaaaaga gttggtagct cttgatccgg caaacaaacc   4260
accgctggta gcggtttttt tgtttgcaag cagcagatta cgcgcagaaa aaaaggatct   4320
caagaagatc ctttgatctt ttctacgggg tctgacgctc agtggaacga aaactcacgt   4380
taagggattt tggtcatgag attatcaaaa aggatcttca cctagatcct tttaaattaa   4440
aaatgaagtt ttaaatcaat ctaaagtata tatgagtaaa cttggtctga cagttaccaa   4500
tgcttaatca gtgaggcacc tatctcagcg atctgtctat ttcgttcatc catagttgcc   4560
tgactccccg tcgtgtagat aactacgata cgggagggct taccatctgg ccccagtgct   4620
```

gcaatgatac cgcgagaccc acgctcaccg gctccagatt tatcagcaat aaaccagcca 4680

gccggaaggg ccgagcgcag aagtggtcct gcaactttat ccgcctccat ccagtctatt 4740

aattgttgcc gggaagctag agtaagtagt tcgccagtta atagtttgcg caacgttgtt 4800

gccattgcta caggcatcgt ggtgtcacgc tcgtcgtttg gtatggcttc attcagctcc 4860

ggttcccaac gatcaaggcg agttacatga tcccccatgt tgtgcaaaaa agcggttagc 4920

tccttcggtc ctccgatcgt tgtcagaagt aagttggccg cagtgttatc actcatggtt 4980

atggcagcac tgcataattc tcttactgtc atgccatccg taagatgctt ttctgtgact 5040

ggtgagtact caaccaagtc attctgagaa tagtgtatgc ggcgaccgag ttgctcttgc 5100

ccggcgtcaa tacgggataa taccgcgcca catagcagaa ctttaaaagt gctcatcatt 5160

ggaaaacgtt cttcggggcg aaaactctca aggatcttac cgctgttgag atccagttcg 5220

atgtaaccca ctcgtgcacc caactgatct tcagcatctt ttactttcac cagcgtttct 5280

gggtgagcaa aaacaggaag gcaaaatgcc gcaaaaaagg gaataagggc gacacggaaa 5340

tgttgaatac tcatactctt cctttttcaa tattattgaa gcatttatca gggttattgt 5400

ctcatgagcg gatacatatt tgaatgtatt tagaaaaata aacaaatagg ggttccgcgc 5460

acatttcccc gaaaagtgcc acctgacgtc 5490

<210> SEQ ID NO 56
<211> LENGTH: 5455
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Vector

<400> SEQUENCE: 56

gacggatcgg gagatctccc gatcccctat ggtgcactct cagtacaatc tgctctgatg 60

ccgcatagtt aagccagtat ctgctccctg cttgtgtgtt ggaggtcgct gagtagtgcg 120

cgagcaaaat ttaagctaca acaaggcaag gcttgaccga caattgcatg aagaatctgc 180

ttagggttag gcgttttgcg ctgcttcgcg atgtacgggc cagatatacg cgttgacatt 240

gattattgac tagttattaa tagtaatcaa ttacggggtc attagttcat agcccatata 300

tggagttccg cgttacataa cttacggtaa atggcccgcc tggctgaccg cccaacgacc 360

cccgcccatt gacgtcaata atgacgtatg ttcccatagt aacgccaata gggactttcc 420

attgacgtca atgggtggag tatttacggt aaactgccca cttggcagta catcaagtgt 480

atcatatgcc aagtacgccc cctattgacg tcaatgacgg taaatggccc gcctggcatt 540

atgcccagta catgacctta tgggactttc ctacttggca gtacatctac gtattagtca 600

tcgctattac catggtgatg cggttttggc agtacatcaa tgggcgtgga tagcggtttg 660

actcacgggg atttccaagt ctccacccca ttgacgtcaa tgggagtttg ttttggcacc 720

aaaatcaacg ggactttcca aaatgtcgta acaactccgc cccattgacg caaatgggcg 780

gtaggcgtgt acggtgggag gtctatataa gcagagctct ctggctaact agagaaccca 840

ctgcttactg gcttatcgaa attaatacga ctcactatag ggagacccaa gctggctagc 900

gtttaaactt aagcttggta ccatggaaca aaaactcatc tcagaagagg atctgggatc 960

cactagtcca gtgtggtgga attctgcaga tatccagcac agtggcggcc gctcgagtct 1020

agagggcccg tttaaacccg ctgatcagcc tcgactgtgc cttctagttg ccagccatct 1080

gttgtttgcc cctcccccgt gccttccttg accctggaag gtgccactcc cactgtcctt 1140

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gggccatcgc cctgatagac ggtttttcgc cctttgacgt tggagtccac gttctttaat 1620

agtggactct tgttccaaac tggaacaaca ctcaacccta tctcggtcta ttcttttgat 1680

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ctccgcccca tggctgacta atttttttta tttatgcaga ggccgaggcc gcctctgcct 2040

ctgagctatt ccagaagtag tgaggaggct tttttggagg cctaggcttt tgcaaaaagc 2100

tcccgggagc ttgtatatcc attttcggat ctgatcaaga gacaggatga ggatcgtttc 2160

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tcggctatga ctgggcacaa cagacaatcg gctgctctga tgccgccgtg ttccggctgt 2280

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tgcaggacga ggcagcgcgg ctatcgtggc tggccacgac gggcgttcct tgcgcagctg 2400

tgctcgacgt tgtcactgaa gcgggaaggg actggctgct attgggcgaa gtgccggggc 2460

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aagagcatca ggggctcgcg ccagccgaac tgttcgccag gctcaaggcg cgcatgcccg 2700

acggcgagga tctcgtcgtg acccatggcg atgcctgctt gccgaatatc atggtggaaa 2760

atggccgctt ttctggattc atcgactgtg gccggctggg tgtggcggac cgctatcagg 2820

acatagcgtt ggctacccgt gatattgctg aagagcttgg cggcgaatgg gctgaccgct 2880

tcctcgtgct ttacggtatc gccgctcccg attcgcagcg catcgccttc tatcgccttc 2940

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Construct

<400> SEQUENCE: 58

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<211> LENGTH: 3890
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Construct

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<210> SEQ ID NO 60
<211> LENGTH: 4131
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Construct

<400> SEQUENCE: 60

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<210> SEQ ID NO 61
<211> LENGTH: 6291
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Construct

<400> SEQUENCE: 61

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Construct

<400> SEQUENCE: 68

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<213> ORGANISM: Artificial Sequence
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The invention claimed is:

1. A DNA construct comprising a nucleic acid sequence encoding a fusion protein comprising a fragment of firefly luciferase fused to at least one fragment of YAP.

2. The DNA construct of claim **1**, wherein the fragment of firefly luciferase comprises amino acids 1-416 of SEQ ID NO:6 and is N-terminal to the at least one fragment of YAP comprising amino acids 120-134 of SEQ ID NO:2.

3. The DNA construct of claim **1**, wherein the fragment of firefly luciferase comprises amino acids 1-544 of SEQ ID NO:6 and is N-terminal to the at least one fragment of YAP comprising amino acids 120-134 of SEQ ID NO:2.

4. A DNA construct comprising a nucleic acid sequence encoding a fusion protein comprising a fragment of firefly luciferase fused to at least one fragment of 14-3-3 protein, wherein the at least one fragment of 14-3-3 protein is capable of binding to YAP.

5. The DNA construct of claim **4**, wherein the at least one fragment of 14-3-3 protein comprises SEQ ID NO:4 and is N-terminal to the fragment of firefly luciferase comprising amino acids 394-550 of SEQ ID NO:6.

6. A DNA construct comprising a nucleic acid sequence encoding a fusion protein comprising a fragment of NanoBiT luciferase fused to at least one fragment of YAP.

7. The DNA construct of claim **6**, wherein the fragment of NanoBit luciferase is LgBiT comprising amino acid sequence SEQ ID NO:52 and is N-terminal to the at least one fragment of YAP comprising amino acids 120-134 of SEQ ID NO:2.

8. A DNA construct comprising a nucleic acid sequence encoding a fusion protein comprising a fragment of NanoBiT luciferase fused to at least one fragment of 14-3-3 protein, wherein the at least one fragment of 14-3-3 protein is capable of binding to YAP.

9. The DNA construct of claim **8**, wherein the at least one fragment of 14-3-3 protein comprises SEQ ID NO:4 and is N-terminal to the fragment of NanoBit luciferase that is SmBiT comprising amino acid sequence SEQ ID NO:54.

10. A DNA construct comprising a nucleic acid sequence encoding a fusion protein comprising a fragment of NanoBit luciferase that is LgBiT comprising amino acid sequence SEQ ID NO:52 and a fragment of YAP comprising amino acids 50-171 of SEQ ID NO:2.

11. A DNA construct comprising a nucleic acid sequence encoding a fusion protein comprising a fragment of NanoBit luciferase that is SmBiT comprising amino acid sequence SEQ ID NO:54 and a fragment of YAP comprising amino acids 50-171 of SEQ ID NO:2.

12. A DNA construct comprising a nucleic acid sequence encoding a fusion protein comprising a fragment of NanoBiT luciferase fused to at least one fragment of TEAD protein, wherein the at least one fragment of TEAD protein is capable of binding to YAP.

13. The DNA construct of claim **12**, wherein the fragment of NanoBit luciferase is LgBiT comprising amino acid sequence SEQ ID NO:52 and the at least one fragment of TEAD protein comprises amino acids 194-411 of SEQ ID NO:50.

14. The DNA construct of claim **12**, wherein the fragment of NanoBit luciferase is SmBiT comprising amino acid sequence SEQ ID NO:54 and the at least one fragment of TEAD protein comprises amino acids 194-411 of SEQ ID NO:50.

* * * * *