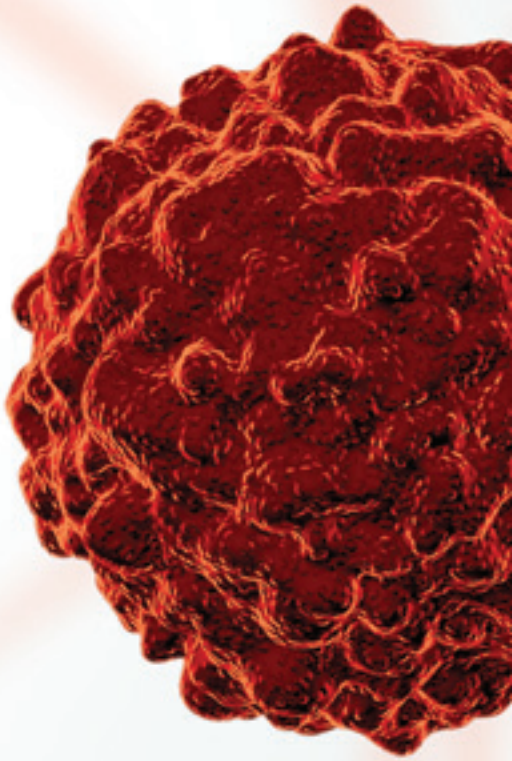
SIGMA Life Science Where bio begins™

Solutions for Cancer Research



Biofiles | Your Biology Resource

Solutions for Cancer Research

As your partner in discovery, we're here to provide you with the information and resources you need to make critical discoveries and stay on the leading edge of cancer research. We have solutions for your cancer research, from our high-quality biochemical reagents to the latest cutting-edge research tools. Our mission is to provide you with the broadest range of cancer research products, backed by unrivaled scientific knowledge and our best-in-class customer and technical service.

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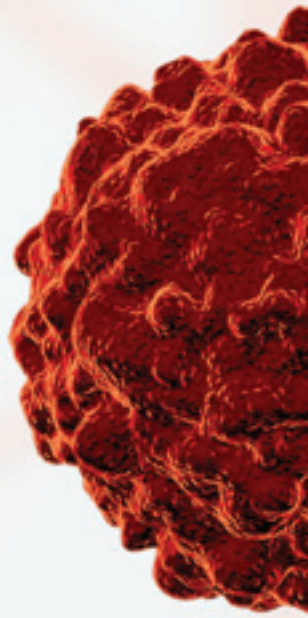

Cellular Analysis

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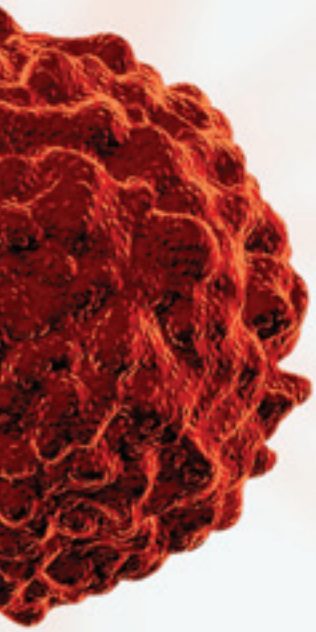


Targeted Gene Analysis

- Inducible shRNA
- miRNA Mimics and siRNA
- miRNA Inhibitors
- WTA Seq
- KiCqStart Primers and Probes and Fast qPCR ReadyMix
- CompoZr Zinc Finger Nucleases
- Prestige Antibodies

CompoZr® Knockout ZFNs

Permanently Knockout Any Human, Mouse, or Rat Gene

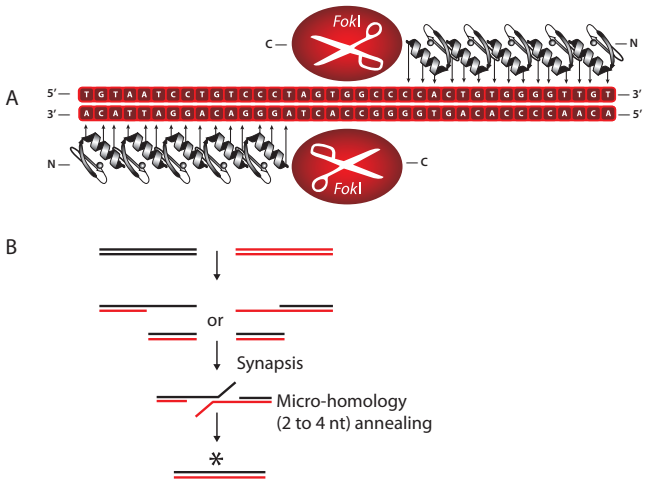
Complete Genomic Coverage

Knockout any gene in the entire human, mouse, or rat genomes with the power of CompoZr Knockout Zinc Finger Nuclease (ZFN) technology from Sigma® Life Science. Access to the proven and award-winning ZFN technology has never been easier. With unprecedented access to all three species, CompoZr Knockout ZFNs are the ideal technology to generate knockout cell lines or research models.

- Zinc finger target sequence is pre-designed in the first available open reading frame site (ORF)
- All Knockout ZFNs are functionally validated prior to shipment
- Immediately transfect cell lines upon receipt of Knockout ZFNs
- Gene editing occurs in 1–20% of clonal population

To learn more, visit
sigma.com/knockout

Zinc Finger-Mediated Gene Knockout

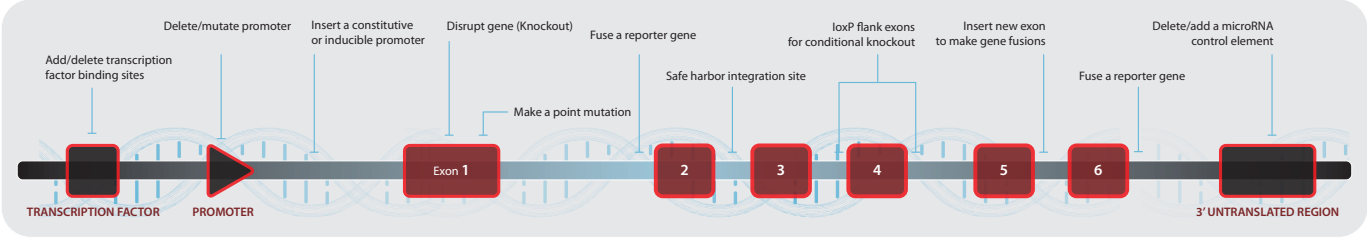


*Mutation due to addition/deletion of bases

ZFN-mediated Targeted Genome Editing (48-72 Hours)
A. The ZFNs bind a specific DNA sequence within the target gene, inducing a double stranded break. **B.** This break is repaired by non-homologous end joining (NHEJ). As an imperfect repair mechanism, a percentage of the double stranded breaks result in nucleotide addition or deletion. These disruptions in DNA sequence result in the loss of functional protein resulting in gene knockout.

The Ability of CompoZr Zinc Finger Nucleases

In addition to gene knockout, CompoZr ZFNs enable researchers to engineer any genome they research in the following ways:



CompoZr® Oncology Disease Model Cell Lines

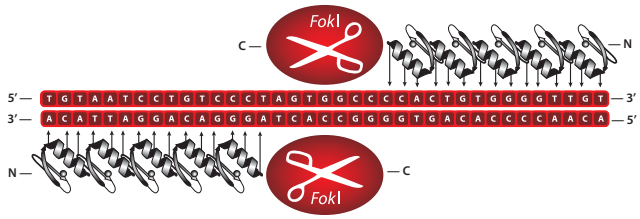
Why Use Disease Model Cell Lines?

- Stable and heritable gene modifications
- Patient-relevant disease mutations in genomic context
- Isogenic setting to study gene function
- Clean genetic modification within genome
- Economical for rapid cell processing and data analysis

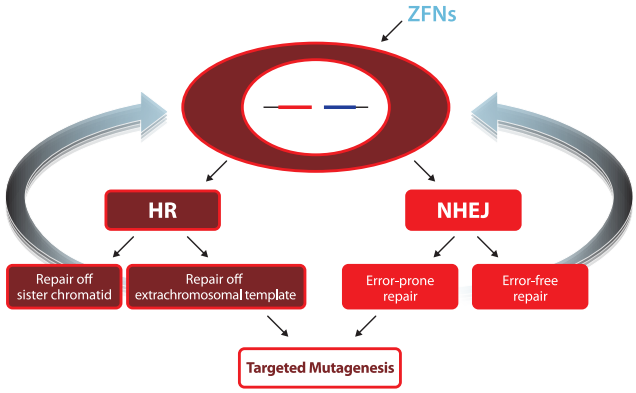
ZFN-modified Human Cells for Colorectal and Lung Cancer Research

Sigma® Life Science proudly introduces a growing portfolio of genetically modified immortalized human cancer cell lines using the revolutionary CompoZr Zinc Finger Nuclease (ZFN) technology. Specific patient-relevant disease modifications have been created in either colorectal adenocarcinoma (DLD1 or SW48) or lung carcinoma (A549) cell lines, and are ideal for applications in areas such as basic research, disease modeling, target validation, and drug discovery and development. These isogenic cell lines provide the tools to take your research to the next level.

A



B



A. Each Zinc Finger Nuclease (ZFN) consists of two functional domains: A DNA-binding domain comprised of a chain of zinc finger modules, each recognizing a unique triplet (3 bp) sequence of DNA. Four to six zinc finger modules are stitched together to form a Zinc Finger Protein (ZFP), with specificity of ≥12 bp. A DNA-cleaving domain comprised of the nuclease domain of *FokI* is attached to the ZFPs. When the DNA-binding and DNA-cleaving domains are fused together, a highly specific pair of 'genomic scissors' is created that binds with 24-36 bp specificity of the ZFPs and cleaves the DNA. **B.** The addition of zinc finger nucleases to the cell results in creation of a double-strand break at the target site. This double-strand break is repaired by one of two endogenous repair pathways, either the non-homologous end joining (NHEJ) or the homologous recombination (HR) pathway. NHEJ is used to create gene knockouts while HR is utilized for targeted integration.

CompoZr Disease Model Cell Lines

Cat. No.	DLD1 Cell Line
CLLS1001-1SET	DLD1 CELLS BAX (-/-)
CLLS1002-1SET	DLD1 CELLS HIF1A (-/-)
CLLS1003-1SET	DLD1 CELLS PIK3CA (+/-)
CLLS1004-1SET	DLD1 CELLS PTEN (-/-)
CLLS1005-1SET	DLD1 CELLS BAX/BAK (-/-,-/-)
CLLS1096-1SET	DLD1 CELLS SMAD4 (-/-)
CLLS1127-1SET	DLD1 CELLS TP53 (-/-)
CLLS1132-1SET	DLD1 CELLS AKT1 (-/-)
CLLS1133-1SET	DLD1 CELLS AKT2 (-/-)
Cat. No.	**SW48 Cell Line**
CLLS1006-1SET	SW48 CELLS BAX (-/-)
CLLS1007-1SET	SW48 CELLS TP53 (-/-)
CLLS1009-1SET	SW48 CELLS PTEN (-/-)
CLLS1010-1SET	SW48 CELLS SMAD4 (-/-)
CLLS1011-1SET	SW48 CELLS BAX/BAK (-/-,-/-)
CLLS1098-1SET	SW48 CELLS HIF1A (-/-/-)
Cat. No.	**A549 Cell Line**
CLLS1012-1SET	A549 CELLS BAX (-/-/-/-)
CLLS1013-1SET	A549 CELLS SMAD4 -/-
CLLS1014-1SET	A549 CELLS HIF1A -/-/-
CLLS1015-1SET	A549 CELLS BAX/BAK (-/-/-/-,-/-)

For more information about Immortalized Cell Lines, visit
sigma.com/biocells

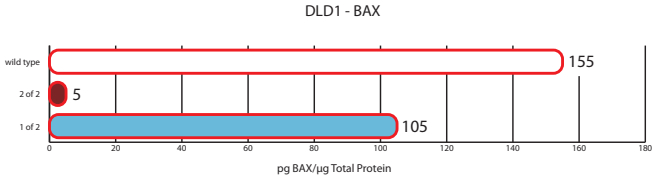
Knockout of Apoptotic Regulators in Cancer Cells

Apoptosis or programmed cell death (PCD) plays an important role in regulating cell proliferation and determining cell fate. Many genes are involved in the apoptotic pathway and deregulation of apoptosis due to gene mutations is implicated in many diseases including a variety of cancers. Two proteins, Bcl2–associated X protein (BAX) and Bcl2-like protein (BAK), are well characterized as pro-apoptotic regulators that play a key role in initiating the PCD pathway. To study the potential role of these proteins in cancer, we created complete gene knockouts of both genes in a human colorectal cancer cell line and examined the response to the apoptotic effector, staurosporine, compared to wild-type control cells.

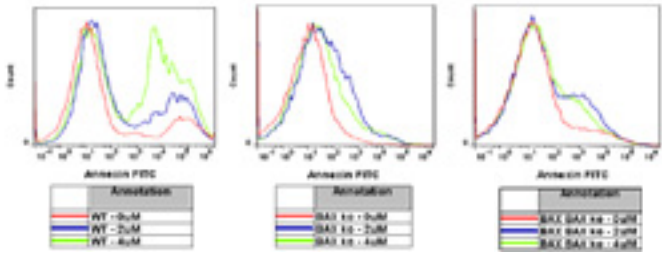
DLD1 BAX (-/-) BAK (-/-)

BAX locus (homologous deletion 63bp)
GTGCACCAAGGTGCCGGAACTGATCAGAACCATCATGGGCTGGACATTGGACTTCCTCCGGGA wt
GT----------A -63
BAK locus (homologous deletion 38bp)
TGCATGCCTCCTGCTCCTACAGCACCATGGGGCAGGTGGGACGGCAGCTCGCCATCATCGGGG wt
TGCATGCCTCCTGC----------CATCATCGGGG -38

DNA Sequence of BAX-BAK Double Knockout in Human DLD1 Cell Line.
CompoZr technology was used to create a homologous BAX-BAK double gene knockout grown out from a single cell clone of DLD1 colorectal carcinoma cells. Sequence analysis confirmed a 63 bp deletion in the BAX locus and a 38 bp deletion in the BAK locus.



BAX Protein Expression in DLD1 Cell Line.
Protein expression was measured in wild-type, monoallelic and biallelic BAX knockout cell lines. Complete knockout of protein expression was only accomplished in the cell line containing the biallelic gene knockout.



Annexin V Cell Staining for Apoptosis in DLD1 Cell Lines.
Each cell line (wild-type, BAX ko, and BAX-BAK ko) was treated with staurosporine then stained using an Annexin V-FITC Apoptosis Detection Kit (APOAF) prior to performing flow cytometry and analysis using Flowjo software. Data show an inhibition of apoptosis in the knockout cell lines compared to wild-type.

CompoZr® Breast Cancer Cell Lines

Disease-Relevant Genetic Knockouts in MCF10A Cells

An individual breast cancer patients' response to therapy may vary depending on their unique genotype and tumor cell subtype characterization. To facilitate research focused on better understanding of the genetics of breast cancer, we have generated a panel of human breast epithelial knockout cell lines that target genes known to be associated with this disease.

Our isogenic breast cancer gene knockout cell line portfolio is created using powerful Zinc Finger Nuclease (ZFN) technology. Individual single-cell clones of MCF10A breast epithelial cells are isolated, characterized, and expanded. Each set includes a vial of modified cells with a vial of the isogenic parental MCF10A control cells.

Breast Cancer Gene Knockout Cell Lines

Cat. No.	Product Name	Gene Symbol	Gene/Protein Function
CLLS1042-1SET	MCF10A CELLS CDH1 (-/-)	CDH1	Calcium-dependent cell adhesion
CLLS1044-1SET	MCF10A CELLS GSK3B (-/-)	GSK3B	Energy metabolism, neuronal cell development
CLLS1045-1SET	MCF10A CELLS HER2 (-/-)	ERBB2; HER2	Receptor tyrosine kinase, cell signaling
CLLS1046-1SET	MCF10A CELLS PTEN (-/-)	PTEN	Tumor suppressor, cell cycle regulation, AKT signaling
CLLS1048-1SET	MCF10A CELLS SYK (-/-)	SYK	Immunoreceptor signaling, proliferation, differentiation
CLLS1049-1SET	MCF10A CELLS TP53 (-/-)	TP53	Cell cycle, DNA repair, apoptosis
CLLS1051-1SET	MCF10A CELLS eEF2K (-/-)	eEF2K	Calmodulin signaling, regulates protein synthesis
CLLS1053-1SET	MCF10A CELLS Rictor (-/-)	Rictor	Cell signaling, cell growth regulation
CLLS1059-1SET	MCF10A CELLS BCR (-/-)	BCR	Kinase activity; translocation site for Philadelphia chromosome
CLLS1060-1SET	MCF10A CELLS CDC25B (-/-)	CDC25B	Phosphatase that regulates cell cycle and mitosis
CLLS1063-1SET	MCF10A CELLS AKT2 (-/-)	AKT2	Oncogene, signal transduction for insulin receptor
CLLS1066-1SET	MCF10A CELLS PARP2 (-/-)	PARP2	Regulation of differentiation, proliferation, tumor transformation
CLLS1069-1SET	MCF10A CELLS APC (-/-)	APC	Tumor suppressor; apopotosis, cell adhesion and migration
CLLS1075-1SET	MCF10A CELLS ESR2 (-/-)	ESR2	Ligand activated transcription factor

Interested in a different cell line?

Purchase the CompoZr ZFNs used to make these cell lines at
sigma.com/knockout

Refer to the Technical Data Sheets for the medium recipe to culture these cell lines, available at
sigma.com/biocells

Why Use CompoZr Breast Cancer Cell Lines?

Genetically-Modified Human Cell Lines with Isogenic Controls

- Complete and permanent loss of the protein
- Targeted gene knockouts, knockins, and point mutations
- Enables complicated genetic studies of gene function in a human cell system
- Pre-neoplastic human mammary epithelial cell line MCF10A used as parental cell line

Patient-relevant Disease Mutations

- Disease-relevant mutations knocked into endogenous locus
- Endogenous protein expression pattern
- Upstream and downstream endogenous regulatory elements are preserved

Robust and Reproducible Results

- Stable and heritable gene modifications
- Consistent results from experiment-to-experiment

Where to Use CompoZr Breast Cancer Cell Lines

Enable Basic Research

- Study gene function in a well-defined genetic system
- Mechanistic studies of disease development, progression, and remission
- Functional assays upon perturbation of specific pathways

Accelerate Drug Discovery

- Patient models for high throughput testing of drug response, resistance, and screening
- Target identification and validation
- Optimization of lead molecules
- Drug repositioning for application to new disease areas

Develop Personalized Therapy

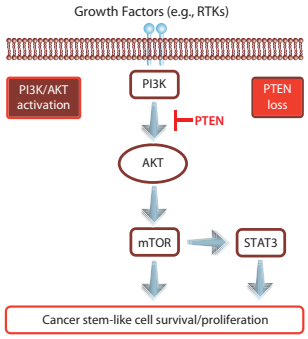
- Identify drug responsive and resistant genotypes in patients
- Determine effective drug combinations to address drug resistance
- Design targeted, less expensive, more successful clinical trials

MCF10A-PTEN Knockout Cells: A Case Study for a Breast Cancer Cell Line

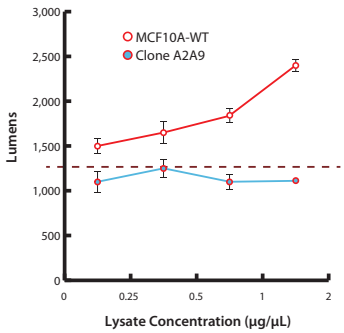
- PTEN (phosphatase and tensin homolog) is a phosphatidyl-inositol-3,4,5-trisphosphate 3-phosphatase and plays a key role in cell cycle regulation
- PTEN preferentially dephosphorylates phosphoinositide substrates and acts as tumor suppressor by negatively regulating AKT/mTOR signaling pathway (A)
- PTEN gene mutations result in activation of phosphatidylinositol 3-kinase (PI3K) pathway, loss of cell cycle control, and development of cancers, including breast cancer[1-3]
- To study the role of PTEN loss in breast cancer, we developed an MCF10A PTEN (-/-) cell line for all aspects of basic research and drug discovery programs
- PTEN protein expression is completely lost in the knockout clone (A2A9) vs. isogenic parental cells (B) providing an ideal cell line to study the PI3K/AKT/mTOR pathway in breast cancer

References:

1. Marty B, Maire V, Gravier E, Rigaill G, Vincent-Salomon A, Kappler M, Lebigot I, Djelti F, Tourdès A, Gestraud P, Hupé P, Barillot E, Cruzalegui F, Tucker GC, Stern MH, Thiery JP, Hickman JA, Dubois T. **Frequent PTEN genomic alterations and activated phosphatidylinositol 3-kinase pathway in basal-like breast cancer cells.** *Breast Cancer Res.* 2008, 10:R101.
2. Nahta R and O'Regan RM. **Evolving strategies for overcoming resistance to HER2-directed therapy: targeting the PI3K/AKT/mTOR pathway.** *Clin Breast Cancer* 2010, 10:S72.
3. Zhou J, Wulfkuhle J, Zhang H, Gu P, Yang Y, Deng J, Margolick JB, Liotta LA, Petricoin E 3rd, Zhang Y. **Activation of the PTEN/mTOR/STAT3 pathway in breast cancer stem-like cells is required for viability and maintenance.** *PNAS* 2007, 104:16158



A. PI3K/AKT/mTOR signaling pathway.[3] PTEN phosphatase activity plays a key role in regulating this critical pathway for controlling cell growth and division.



B. Following treatment of MCF10A cells with ZFNs specific for PTEN gene, a clone (A2A9) was isolated that contained a unique biallelic disruption of the genomic sequence.

PTEN protein concentration was measured in wild-type (WT) and knockout cell lines using an enzyme immunometric assay specific for PTEN. Whereas, PTEN protein levels increased with increasing amounts of WT lysate added to the assay, PTEN protein remained at background levels in the ZFN-modified cell line.

Selected Cell Lines for Cancer Research

Cancer is a complex phenomenon. A specific type of cancer can vary in terms of markers and disease affected pathways from patient to patient or even from cell to cell within a specific tumor.[1-3] Established cell lines provide a valuable tool in limiting the variables, allowing the study of specific pathways and causes. Today cell lines are used in the study of carcinogenesis,[4] chemoprevention,[5] cell signaling, and drug sensitivity.[6]

Sigma® Life Science has partnered with the European Collection of Cell Cultures (ECACC) to offer a variety of cancer-derived cell lines. All cell lines have been authenticated and are mycoplasma tested. Sigma Life Science offers these and other cell lines to ensure you have the right tools to facilitate the complex task of cancer research. For a more extensive listing of cell lines, visit **sigma.com/ecacc.**

References:

1. Park, S.Y., et al., Cellular and genetic diversity in the progression of *in situ* human breast carcinomas to an invasive phenotype. *J. Clin. Invest.*, **120**, 636–644 (2010).
2. Heppner, G.H., et al., Mammary tumor heterogeneity. *Symp. Fundam. Cancer Res.*, **36**, 209–221 (1983).
3. Heppner, G.H. and Miller, B.E., Tumor heterogeneity: biological implications and therapeutic consequences. *Cancer Metastasis Rev.*, **2**, 5–23 (1983).
4. Pilli, T., et al., Potential utility and limitations of thyroid cancer cell lines as models for studying thyroid cancer. *Thyroid*, **19**, 1333–42 (2009).
5. Cuendet, M., et al., Quinone reductase induction as a biomarker for cancer chemoprevention. *J. Nat. Prod.*, **69**, 460–463 (2006).
6. Sharma, S.V., et al., Cell line-based platforms to evaluate the therapeutic efficacy of candidate anticancer agents. *Nat. Rev. Cancer*, **10**, 241–53 (2010).

Cancer Cell Lines

Name	Description	Biological Source	Cat. No.
A2780ADR Cell Line	Human Caucasian ovarian carcinoma	human	93112520-1VL
A2780 Cell Line	ovarian carcinoma	human	93112519-1VL
A2780cis Cell Line	ovarian carcinoma	human	93112517-1VL
A375-C5 Cell Line	Human malignant melanoma IL-1 insensitive	human	97011320-1VL
A375 Cell Line	Human malignant melanoma	human	88113005-1VL
A431 Cell Line	squamous carcinoma	human	85090402-1VL
A549 Cell Line	human lung carcinoma	human	86012804-1VL
AGS Cell Line	Human Caucasian gastric adenocarcinoma	human	89090402-1VL
B16-F0 Cell Line	Mouse melanoma, producing melanin	from mouse	92101204-1VL
B16-F1 Cell Line	Mouse melanoma, producing melanin	from mouse	92101203-1VL
B16 melanoma 4A5 Cell Line	Mouse melanoma, producing melanin	from mouse	94042254-1VL
BXPC3 Cell Line	Human primary pancreatic adenocarcinoma	human	93120816-1VL
C6 Cell Line	Rat glial tumor	from rat	92090409-1VL
CACO-2 Cell Line	Caucasian colon adenocarcinoma	human	86010202-1VL
1301 Cell Line	Tcell leukemia	human	01051619-1VL
1321N1 Cell Line	Glial cells from brain astrocytoma	human	86030402-1VL
COLO 205 Cell Line	Human Caucasian colon adenocarcinoma	human	87061208-1VL
DAUDI Cell Line	African-American Burkitt's lymphoma	human	85011437-1VL
EL4 Cell Line	Lymphoblast from blood	murine	85023105-1VL
FTC-133 Cell Line	Human follicular thyroid carcinoma	human	94060901-1VL
HCT 116 Cell Line	colon carcinoma	human	91091005-1VL
HeLa Cell Line	epitheloid cervix carcinoma	human	93021013-1VL
Hep-2C Cell Line	human cervix carcinoma (HeLa derivative)	human	85020207-1VL
Hep2(HeLa derivative) Cell Line	Human Black cervix carcinoma	human	86030501-1VL
Hep G2 Cell Line	hepatocyte carcinoma	human	85011430-1VL

Name	Description	Biological Source	Cat. No.
HL60 Cell Line	Caucasian promyelocytic leukemia	human	98070106-1VL
HT29 Cell Line	Caucasian colon adenocarcinoma grade II	human	91072201-1VL
HT55 Cell Line	Human colon carcinoma	human	85061105-1VL
Huh-7D 12 Cell Line	Human hepatocellular carcinoma	human	01042712-1VL
Ishikawa Cell Line	endometrial adenocarcinoma	human	99040201-1VL
J774.2 Cell Line	Balb/C monocyte macrophage	from mouse	85011428-1VL
Jurkat E6.1 Cell Line	leukemic T cell lymphoblast	human	88042803-1VL
K1 Cell Line	Human thyroid carcinoma	human	92030501-1VL
K562 Cell line	chronic myelogenous leukemia	human	89121407-1VL
KELLY Cell Line	neuroblastoma	human	92110411-1VL
LNCap Clone FGC Cell Line	prostate carcinoma	human	89110211-1VL
LoVo Cell Line	Human colon adenocarcinoma	human	87060101-1VL
MCF7 Cell Line	breast adenocarcinoma	human	86012803-1VL
MDA-MB-231 Cell Line	human breast adenocarcinoma	human	92020424-1VL
MG-63 Cell Line	Human osteosarcoma	human	86051601-1VL
U-87 MG Cell Line	glioblastoma astrocytoma	human	89081402-1VL
Nb2-11 Cell Line	Thymus/lymph node, lymphoblast morphology	from rat	97041101-1VL
NCI-H322 Cell Line	Human Caucasian bronchioalveolar carcinoma	human	95111734-1VL
NTERA-2 clone D1 Cell Line	caucasian pluripotent embryonal carcinoma	human	01071221-1VL
OAW28 Cell Line	ovarian tumor epithelial	human	85101601-1VL
OE19 Cell Line	Human oesophagus/gastric cardia	human	96071721-1VL
OE21 Cell Line	Human Caucasian esophageal squamous cell carcinoma	human	96062201-1VL
OE33 Cell Line	Human Caucasian esophageal carcinoma	human	96070808-1VL
U-2 OS Cell Line	osteosarcoma	human	92022711-1VL
P19 Cell Line	Mouse teratocarcinoma	from mouse	95102107-1VL
PANC-1 Cell Line	Caucasian pancreas	human	87092802-1VL
PC-3 Cell Line	Caucasian prostate adenocarcinoma	human	90112714-1VL
RAJI Cell Line	Human Black Burkitt's lymphoma	human	85011429-1VL
RAMOS Cell Line	Human Caucasian Burkitt's lymphoma	human	85030802-1VL
RAW 264.7 Cell Line	Macrophage from blood	murine	91062702-1VL
RAW 264 Cell Line	Mouse leukemic monocyte-macrophage	from mouse	85062803-1VL
RPMI 8866 Cell Line	Lymphoblastoid from blood	human	95041316-1VL
SAOS-2 Cell Line	primary osteogenic sarcoma	human	89050205-1VL
SH-SY5Y Cell Line	Neuroblast from neural tissue	human	94030304-1VL
SK-OV-3 Cell Line	Human Caucasian ovary adenocarcinoma	human	91091004-1VL
SW480 Cell Line	Human colon adenocarcinoma	human	87092801-1VL
SW 620 Cell Line	Human Caucasian colon adenocarcinoma	human	87051203-1VL
T47D Cell Line	Human breast tumor	human	85102201-1VL
T84 Cell Line	Human colon carcinoma	human	88021101-1VL
T98G Cell Line	Human Caucasian glioblastoma	human	92090213-1VL
TF1 Cell Line	Erythroleukemic cell line from blood	human	93022307-1VL
THP 1 Cell Line	Leukemic monocyte	human	88081201-1VL
U937 Cell Line	Lymphoblast from lung	human	85011440-1VL
VCaP Cell Line	Human prostate cancer metastasis	human	06020201-1VL

Cell Design Studio™

CompoZr® ZFN Modified Cells

Why Use Our Cell Design Studio (CDS)?

- **Easy** access to CompoZr ZFN Technology
- **Rapid** delivery of modified cell lines in as little as 20 weeks
- **Efficient** use of your resources – no additional resources, training, or capital equipment is required
- **Ready-to-use** modified cell lines delivered to you
- **Dedicated and Experienced** custom cell engineering team will work closely with you to develop your cell line

Project Initiation and Inquiry

Inquiries are initiated through the CompoZr Custom ZFN Application Form. Please indicate that you want CDS services in question eight.

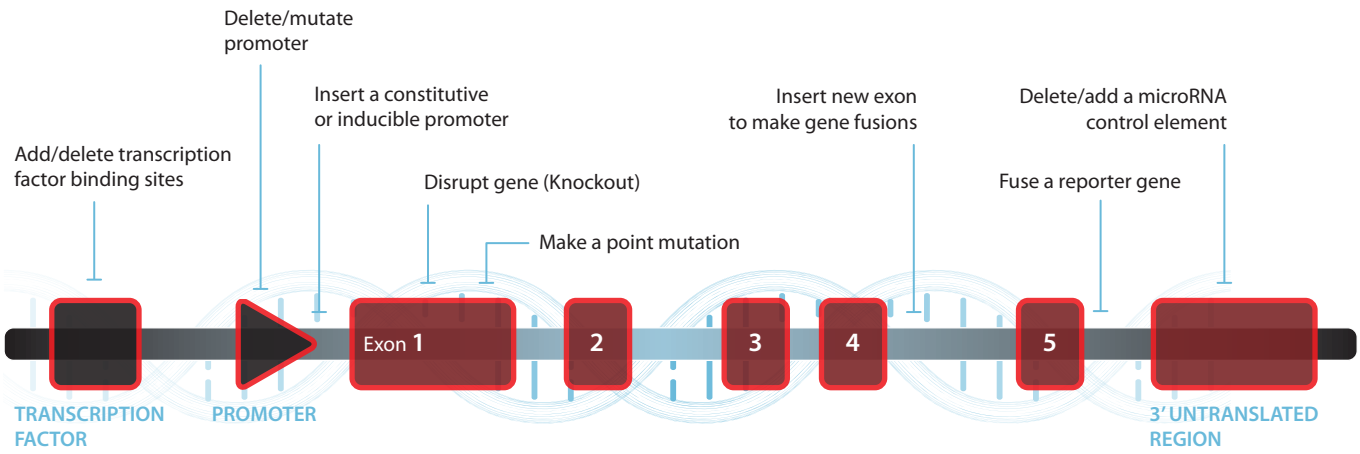
To access the form, visit
sigma.com/biocells

Designer Genomes with ZFN-Modified Cell Lines from CDS

The Cell Design Studio from Sigma® Life Science leverages several molecular biology techniques, most notably CompoZr Zinc Finger Nuclease Technology (see Project Types below) to genetically engineer mammalian cell lines to your specifications. Utilize our expertise to create gene knockouts, knockins, and gene corrections in your cell line for use in any area of basic research, cell-based assays, target validation, drug discovery, and drug development.

For more information about CompoZr ZFNs, visit
sigma.com/zfn

Project Types



Examples of genetically engineered cell line projects that are possible with CompoZr ZFN technology

Project Phases

CDS projects are divided into phases.

Phase 0
(8 - 10 weeks)

- ZFN design, assembly, validation
- Donor design (for knockin projects)

Phase I
(2 - 3 weeks)

- Cell line transfer
- Transfection
- ZFN activity confirmation in transfected pool

Phase II
(8 - 10 weeks)

- Single cell cloning and sequence verification
- Clone expansion
- Cryopreservation
- Documentation package (optional)

Phase III
(6 weeks)

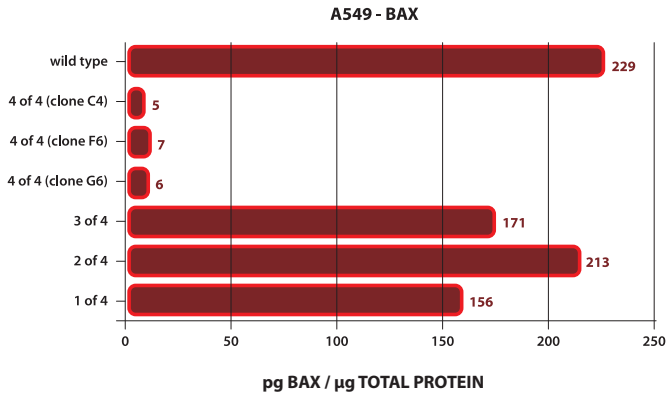
- Growth and productivity assay
- Transcript or protein level assessment
- Recombinant protein secretion assessment

For more project examples, visit
sigma.com/biocells

Project Example

Objective: Inactivate the apoptotic gene BAX, which is tetraploid in A549 cells.

Results: Using ZFN-mediated gene deletion, a range of single and multi-allelic BAX knockout cell lines were generated.



BAX protein concentration was measured in wild type and knockout cell lines using an enzyme immunometric assay specific for BAX. Quantification of BAX protein levels was obtained through comparison of BAX protein levels in the cell lysate to a standard curve of recombinant BAX protein. Clones having 1-, 2- or 3-out-of-4 alleles disrupted produce less BAX protein. For three unique clones, each with all 4 alleles disrupted, the measurement was below the lower limit of detection demonstrating no BAX protein is produced when 4-out-of-4 alleles are disrupted. Clones with 1-, 2- or 3-of-4 alleles disrupted produce less BAX protein (The linear detection limit for the assay is at 15 pg). Data provided by Suzanne Hibbs and Gregory Wemhoff, Ph.D., at Sigma® Life Science.

Project Deliverables

- CompoZr® Zinc Finger Nuclease Kit
  - Plasmid DNA
  - mRNA
  - Primers
- 5 vials of engineered cell lines
  - May include multiple clones
- 5 vials of parental cell line (upon request)
- Full Project Report
  - History of cell handling
  - Reagents used
  - Sequence data
  - Safety and QC test results
  - Other requested data

CompoZr® Cellular Reporter Cell Lines

Why Use CompoZr Cellular Reporter Cell Lines?

- **Easy visualization of live cells**
  - Fluorescently tagged cytoskeletal proteins
- **Endogenous protein expression pattern**
  - Tagged proteins driven by endogenous promoters
  - Upstream and downstream regulatory elements are preserved
  - Copy number is kept constant
- **Save time and money**
  - Replace extensive antibody optimization
  - Eliminate staining artifacts
  - Reduce hands-on time for staining manipulations and molecular verification
- **Robust and reproducible results**
  - Stable and heritable gene modification
  - Consistent results from experiment-to-experiment

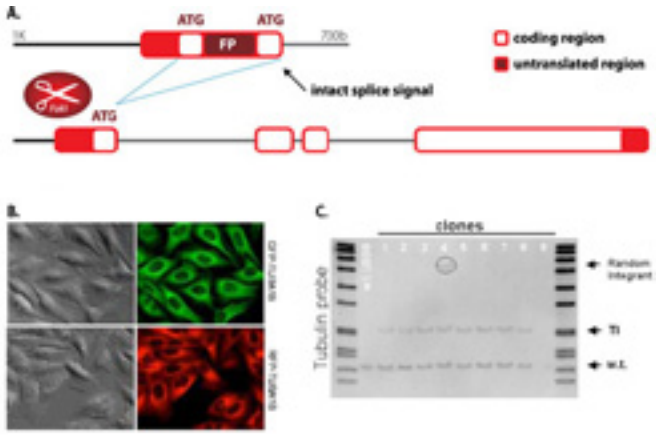
Where to Use CompoZr Cellular Reporter Cell Lines

- **Observe and assay perturbations to live cellular systems**
  - In protein localization and function
  - In gene regulation
  - High-throughput and high-content screening

CompoZr Cellular Reporter Cell Lines

The study of gene function has long been limited by the use of over-expression systems and by tedious staining procedures. To enable scientists to study protein function and protein localization in a live cellular system, we have generated engineered human U2OS cell lines in which several genes are fluorescently tagged at the endogenous loci.

This range of genetically modified mammalian cell lines was generated using the revolutionary CompoZr Zinc Finger Nuclease (ZFN) technology (sigma.com/zfn), for use in areas such as basic research, live protein visualization, and to serve as a base cell line for high throughput screening. With targeted and heritable stable gene integrations our isogenic cell lines give you the tools to take your research to new heights.



U2OS cell lines with TUBA1B tagged with green fluorescent protein (GFP) and red fluorescent protein (RFP) at the endogenous locus. (A) Schematic of the TUBA1B locus and donor. **(B)** Images of endogenously labeled TUBA1B with GFP and RFP in U2OS cells. **(C)** Southern hybridizations were performed on DNA isolated from wild-type U2OS and nine single cell clones positive for red tubulin fluorescence.

For more about the CompoZr Cellular Reporter Cell Lines, visit
sigma.com/biocells

For more about the CompoZr ZFN technology used to make these cells, visit
sigma.com/zfn

CompoZr Cellular Reporter Cell Lines

Cat. No.	Cell Line	Gene Target(S)	Human Gene ID	Protein Function
CLL1031-1VL	U2OS GFP-TUBA1B	TUBA1B	10376	Globular protein - microtubule dynamics
CLL1032-1VL	U2OS GFP-ACTB	ACTB	60	Cytoskeletal protein - cell motility
CLL1033-1VL	U2OS GFP-LMNB1	LMNB1	3912	Nuclear protein - nuclear stability and gene expression
CLL1034-1VL	U2OS RFP-TUBA1B	TUBA1B	10376	Globular protein - microtubule dynamics
CLL1035-1VL	U2OS RFP-ACTB	ACTB	60	Cytoskeletal protein - cell motility
CLL1036-1VL	U2OS GFP-HMGA1	HMGA1	3159	Non-histone protein - regulation of gene expression
CLL1037-1VL	U2OS GFP-ACTB RFP-TUBA1B	ACTB / TUBA1B	60 / 10376	Cytoskeletal protein - cell motility; Globular protein - microtubule dynamics
CLL1038-1VL	U2OS BFP-LMNB1 RFP-ACTB	LMNB1 / ACTB	3912 / 60	Nuclear protein - nuclear stability and gene expression; Cytoskeletal protein - cell motility
CLL1039-1VL	MCF10A RFP-TUBA1B	TUBA1B	10376	Globular protein - microtubule dynamics
CLL1135-1VL	SKOV3 GFP-HER2	HER2	2064	EGF receptor 2 – forms heterodimers with other EGF receptors to mediate downstream signaling pathways
CLL1136-1VL	U2OS GFP-NUP98	NUP98	4928	Nucleoporin 98 kDa protein – protein in nuclear pore complex
CLL1139-1VL	SKOV3 GFP-STAT3	STAT3	6774	Transcription factor – regulates nuclear gene expression
CLL1140-1VL	A549 RFP-STAT3	STAT3	6774	Transcription factor – regulates nuclear gene expression
CLL1141-1VL	A549 GFP-EGFR	EGFR	1956	EGF receptor 1 – cell surface protein, binds epidermal growth factor, dimerizes and stimulates downstream signaling to promote proliferation
CLL1143-1VL	SKOV3 GFP-HER2 RFP-EGFR	HER2 EGFR	2064 / 1956	EGF receptor 2 – forms heterodimers with other EGF receptors to mediate downstream signaling pathways / EGF receptor 1 – cell surface protein, binds epidermal growth factor, dimerizes and stimulates downstream signaling to promote proliferation
CLL1149-1VL	A549 GFP-CTNNB1 RFP-LMNB1	CTNNB1 / LMNB1	1499 / 3912	β-catenin – protein in adherens junction, involved in regulation of cell adhesion and growth / Nuclear protein – nuclear stability and gene expression
CLL1158-1VL	A549 GFP-STAT1	STAT1	6772	Transcription factor – regulates nuclear gene expression
CLL1167-1VL	A549 GFP-SMAD4	SMAD4	4089	Transcription factor – regulates nuclear gene expression
CLL1218-1VL	U2OS LMNB1-TUBA1B-ACTB	LMNB1 / TUBA1B / ACTB	3912 / 10376 /60	Nuclear protein – nuclear stability and gene expression / Globular protein – microtubule dynamics / Cytoskeletal protein – cell motility

We recommend the following culture media components for use with our cell lines:

- U2OS cell lines
  - M9309 – McCoy's 5A Medium Modified
  - F2442 – Fetal Bovine Serum
  - C6164 – Cell Freezing Medium-DMSO
- MCF10A cell lines
  - 51448C – Dulbecco's Modified Eagle's Medium/Ham's Nutrient Mixture F-12
  - H1270 – Horse Serum
  - C8052 – Cholera Toxin (*Vibrio cholerae*)
  - I9278 – Insulin solution human (recombinant)
  - E9644 – Epidermal Growth Factor human
  - H6909 – Hydrocortisone solution
  - G3126 – L-Glutamine
  - C6164 – Cell Freezing Medium-DMSO
- A549 cell lines
  - R0883 – RPMI-1640 Medium
  - F2442 – Fetal Bovine Serum
  - G7513 – L-Glutamine
  - C6164 – Cell Freezing Medium-DMSO
- SKOV3 cell lines
  - M8403 – McCoy's 5A Medium
  - F2442 – Fetal Bovine Serum
  - G7513 – L-Glutamine
  - C6164 – Cell Freezing Medium-DMSO

Interested in a Different Cell Line?

Purchase the CompoZr Knockout ZFNs used to make these cell lines at **sigma.com/knockout**

Refer to the Technical Data Sheets for the medium recipe to culture these cell lines, available at **sigma.com/biocells**

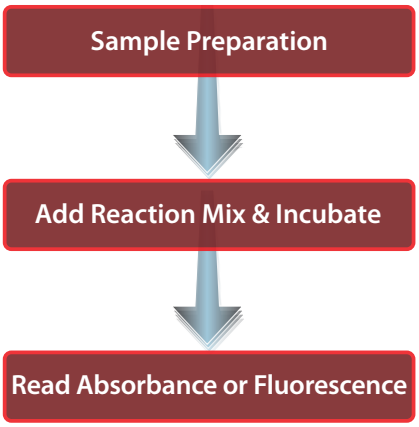
Cancer Metabolism Assay Kits

Convenient Assay Kits to Analyze Metabolites and Enzymes

Features and Benefits

- Convenient, simple, and highly-dependable assays for monitoring key cancer metabolic pathways
- Assay kits utilize spectrophotometric, fluorimetric, and/or gravimetric detection methods
- Contain all necessary components and reagents for analysis
- Most assay kits are suitable for high-throughput assays

General Assay Design



For more information, visit
sigma.com/assaykits

Assay Kits for Quantification of Cancer Metabolism Metabolites and Enzymes

Sigma® Life Science offers a wide range of kits for analyzing both critical metabolites and the activity of key metabolic enzymes.

Cat. No.	Product Name
Aerobic Glycolysis Assay Kits	
MAK039	Acetyl-Coenzyme A Assay Kit
MAK020	Fructose-6-Phosphate Assay Kit
MAK014	Glucose-6-Phosphate Assay Kit
MAK021	High Sensitivity Glucose-6-Phosphate Assay Kit
MAK064	Lactate Assay Kit
MAK065	Lactate Assay Kit II
MAK066	Lactate Dehydrogenase Activity Assay Kit
MAK067	Malate Assay Kit
MAK037	NAD/NADH Quantitation Kit
MAK071	Pyruvate Assay Kit
MAK072	Pyruvate Kinase Activity Assay Kit
Glutamine Metabolism Assay Kits	
MAK039	Acetyl-Coenzyme A Assay Kit
MAK001	Alanine Assay Kit
AA0100	Ammonia Assay Kit
MAK034	Coenzyme A (CoA) Assay Kit
MAK035	FAD Assay Kit
MAK060	Fumarate Assay Kit
MAK004	Glutamate Assay Kit
GLN1	Glutamine and Glutamate Determination Kit
MAK061	Isocitrate Assay Kit
MAK054	α-Ketoglutarate Assay Kit
MAK037	NAD/NADH Quantitation Kit
MAK070	Oxaloacetate Assay Kit
Fatty Acid Metabolism Assay Kits	
MAK039	Acetyl-Coenzyme A Assay Kit
AA0100	Ammonia Assay Kit
MAK063	L-Carnitine Assay Kit
MAK057	Citrate Assay Kit
MAK034	Coenzyme A (CoA) Assay Kit
MAK038	NADP/NADPH Quantitation Kit
MAK070	Oxaloacetate Assay Kit
ML0010	TCA Cycle Metabolite Library
Mevalonate Pathway Assay Kits	
MAK043	Cholesterol Quantitation Kit
CS1090	HMG-CoA Reductase Assay Kit
Isocitrate Dehydrogenase (IDH) Pathway Assay Kits	
MAK062	IDH Pathway Assay Kit
MAK061	Isocitrate Assay Kit
MAK054	α-Ketoglutarate Assay Kit
MAK038	NADP/NADPH Quantitation Kit
Nucleotide Synthesis Metabolism Assay Kits	
MAK015	Glucose-6-Phosphate Dehydrogenase Activity Assay Kit
MAK038	NADP/NADPH Quantitation Kit

Library of Pharmacologically Active Compounds (LOPAC®,[1280])

Predictable Activities and Proven Scaffolds

The power and performance of the bioactive small molecules in Sigma® Life Science's Library of Pharmacologically Active Compounds (LOPAC[1280]) is assured. This biologically annotated collection of inhibitors, receptor ligands, and approved drugs impacts most signaling pathways and covers all major drug target classes.

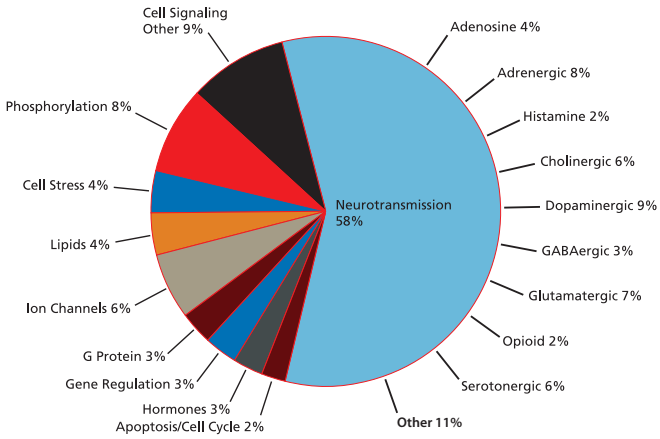
- **1,280 pharmacologically active compounds** – All major target classes are represented, including GPCRs and kinases, making LOPAC the most flexible target characterization and assay validation library available
- **Marketed drugs and pharmaceutically relevant structures annotated with biological activities** – Predictable activities and proven scaffolds directed against a wide range of drug targets to guide repurposing applications
- **Pre-solubilized and normalized compounds to guide repurposing applications** – Ready-to-use DMSO stocks require less time-consuming sample preparation
- **Guaranteed Sigma quality and easy re-supply** – Highly pure compounds, each available as an individual catalog item

Relevant Compounds and Pharmacological Activities

- Antiproliferatives
- Enzyme inhibitors
- Approved drugs
- Cell cycle regulators
- Apoptosis inducers
- GPCR ligands

LOPAC[1280] compounds are also indexed in the NCBI's PubChem database.

Search for compounds that modulate your target at
sigma.com/bioactivity



LOPAC[1280]

Format: 250 µL at 10 mM in DMSO
Cat. No: LO1280 (LO3300 outside the U.S.)

LOPAC[1280] – Small Scale

Format: 25 µL at 10 mM in DMSO
Cat. No: LO4100 (LO4200 outside the U.S.)

Compounds are arranged in 96-well format in 16 racks of 80, one compound per well.

To request a complete list of components, visit
sigma.com/bioactivity

LOPAC in the Literature

- Jo, Y.K., et al., ARP1, a selective MMP-2 inhibitor, induces autophagy-associated cell death in cancer cells. *Biochem. Biophys. Res. Comm.*, 404:1039 (2011).
- Finlay, D., et al., Novel HTS Strategy Identifies TRAIL-Sensitizing Compounds Acting Specifically Through the Caspase-8 Apoptotic Axis. *PLoS ONE* 5(10): e13375 (2010).
- Lucumi, E., et al., Discovery of Potent Small-Molecule Inhibitors of Multidrug-Resistant *Plasmodium falciparum* Using Novel Miniaturized High-Throughput Luciferase-Based Assay. *Antimicrobial Agents and Chemotherapy*, 54(9):3597 (2010).
- Kota, S., et al., A Time-Resolved Fluorescence-Resonance Energy Transfer Assay for Identifying Inhibitors of Hepatitis C Virus Core Dimerization. *Assay Drug Dev. Tech.*, 8(1):96 (2010).
- Diamandis, P., et. al., Chemical genetics reveals a complex functional ground state of neural stem cells. *Nat. Chem. Biol.*, 3(5):268 (2007).
- Lazo, J.S., et. al., Building a Pharmacological Lexicon: Small Molecule Discovery in Academia. *Mol. Pharmacol.*, 72:1 (2007).

Bioactive Small Molecules for Cancer Research

Developed by Pfizer

Pfizer Drugs and Literature Compounds

At Sigma® Life Science, the Pfizer pipeline is your pipeline. Sigma and Pfizer are working together to provide you access to many of Pfizer's well known compounds. To date, we offer over 100 of their bioactive small molecules including 30 established drugs. The table below lists compounds from the Pfizer collection that are relevant to cancer research.

Cat. No.	Compound	Bioactivity
PZ0006	Exemestane	Steroidal antiestrogen and irreversible aromatase inhibitor
PZ0012	Sunitinib	Receptor tyrosine kinase inhibitor
PZ0020	Temsirolimus	mTOR Complex 1 (mTORC1) inhibitor
PZ0107	CP-101537	Matrix metalloproteinase (MMP) inhibitor
PZ0108	CP-335963	Aurora 2 kinase inhibitor
PZ0109	PD-161570	Human FGF-1 receptor tyrosine kinase inhibitor
PZ0111	PD-407824	Wee1/Chk1 inhibitor
PZ0112	PD-184161	MEK inhibitor
PZ0113	PD173952	Src family kinase inhibitor
PZ0114	PD-166866	FGF-1 receptor tyrosine kinase (FGFR1) inhibitor
PZ0115	CP-31398	p53 stabilizer; apoptosis inducer
PZ0116	PD-166285	Broad spectrum protein tyrosine kinase inhibitor
PZ0117	PF-573228	Focal adhesion kinase (FAK) inhibitor
PZ0118	Nafoxidine	Potent estrogen receptor antagonist
PZ0129	CP-380736	Epidermal growth factor receptor (EGFR) inhibitor
PZ0130	CP-64434	Histone deacetylase (HDAC) inhibitor
PZ0137	CP-471474	Broad spectrum matrix metalloproteinase inhibitor
PZ0140	EBPC	Aldose reductase inhibitor; activates extracellular signal-regulated kinases
PZ0142	PD-180970	p210Bcr-Abl tyrosine kinase inhibitor
PZ0143	PF-4708671	First selective p70 ribosomal S6 kinase (S6K1) inhibitor
PZ0147	PHA-665752	c-Met kinase inhibitor
PZ0150	SU5614	FMS-like tyrosine kinase 3 (FLT3) inhibitor
PZ0151	PF-956980	FGF1 receptor antagonist
PZ0152	UK-356,618	Inhibitor of Matrix metalloproteinase MMP3 (stromelysin-1)
PZ0162	PD0325901	Selective MEK1/2 inhibitor
PZ0178	PHA 767491	ATP-competitive dual inhibitor cdc7/cdk9
PZ0181	PD184352	MEK (MKK1, MAPK kinase) inhibitor
PZ0183	ERB-041	Estrogen ERβ receptor agonist
PZ0186	PF-477736	ATP-competitive small-molecule inhibitor of Chk1
PZ0192	Bosutinib	Dual Src/Abl tyrosine kinase inhibitor
PZ0193	Axitinib	Potent, selective tyrosine kinase inhibitor that blocks VEGF receptors 1, 2, and 3
PZ0198	Prinomastat hydrochloride	MMP inhibitor
PZ0199	PD 0332991 Isethionate	Potent and selective CDK4/CDK6 inhibitor

NEW from Sigma Life Science!
LOPAC®, Pfizer

The Hottest Pfizer-Developed Drugs and Inhibitors in Ready-to-Screen Format

The power and convenience of LOPAC[1280], the gold-standard collection of receptor ligands and drugs, has been extended to our Pfizer compounds. For the first time sutent, bosutinib, axitinib, and many other cancer-related compounds are available in ready-to-screen format for your convenience.

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- Pre-solubilized at 10 mM in DMSO (96-well format)
- Biological activities for every compound
- Authentic Pfizer material backed by a Sigma-Aldrich quality inspection

To request a list of library components for this and other LOPAC collections, visit
sigma.com/lopacsfn

Product Number: LO5100-1EA
Product Name: LOPAC[Pfizer]
Sold for research purposes under agreement from Pfizer, Inc.

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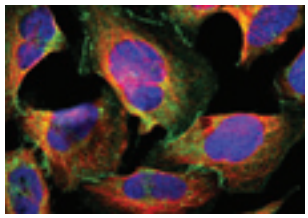
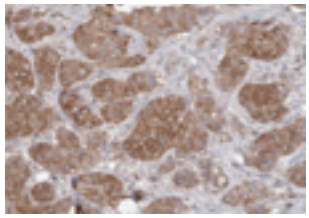


Staining of intercellular junction in U2OS cells with organelle specific Prestige Antibody anti-tight junction protein 1 (Zonula occludens 1). Protein targeted by antibody is shown in green, nucleus in blue, micro-tubules in red, and endoplasmatic reticulum (ER) in yellow. **Cat. No.** HPA001636



Breast Cancer tissue stained with anti-MTHFD1. Brown color indicates presence of protein, blue color shows cell nuclei. **Cat. No** HPA000704

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Duolink® PLA® Technology

Powered by Sigma® Life Science

Accelerate the Signaling Pathway Discovery Process

Detect, quantify, and determine cell localization of a specific protein complex in the same experiment. Duolink, which is based on the *in situ* PLA technology, enables you to visualize protein interactions in fixed cells and tissue samples, all while under endogenous protein expression.

- Visualize individual interactions without having to overexpress proteins
- Gain high specificity with dual binding of primary antibodies
- Single molecule sensitivity due to signal amplification
- Analyze using standard immunofluorescence instruments

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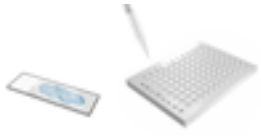
The Duolink kit series of optimized, simple to use reagents, allows the user to combine any pair of immunofluorescence or immunohistochemistry validated antibodies for direct in-cell detection of protein interaction events. Duolink read-out is performed either with a fluorescent label for fluorescence microscopy or HRP for brightfield detection. The resulting distinct spots are derived from individual protein interaction events, which are visualized using a standard microscope.

Preparation



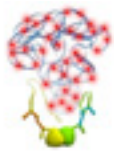
STEP 1. Fix cells or tissues onto microscope slide or microplate.

STEP 2. Wash and add two primary antibodies.

STEP 3. Wash and add the PLUS and MINUS PLA probes.

Detection

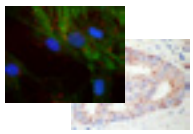
STEP 4. Wash and add Ligation solution.



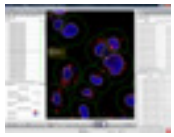
STEP 5. Wash and add Amplification solution.

STEP 6. Review and capture images.

Analysis



STEP 7. Single protein interactions visualized using fluorescence and brightfield, respectively.



STEP 8. Obtain objective quantification using Duolink Image Tool.

STEP 9. Data analysis.

Cells or tissue deposited on slides or in microplates are fixed (Step 1) to preserve activation status and transient interactions. Validated primary antibodies for the targets are added (Step 2) followed by Duolink secondary PLA probes (Step 3). Detection is performed by forming a reporter substrate based on the proximity of the two primary antibodies used (Step 4) followed by amplification (Step 5).

The result is visualized using a standard microscope (Steps 6 and 7). The resulting images can easily be quantitatively analyzed using Duolink Image Tool software (Step 8), which facilitates both average and single cell data analysis (Step 9).

Duolink *In Situ* Product List

To perform a Duolink assay a PLA probe PLUS, a PLA probe MINUS and a Detection Reagent are required. Recommended accessories are Wash Buffers and Mounting Medium.

Cat. No.	Product Description	Size
PLA Probes PLUS		
DUO92001	Duolink In Situ PLA probe anti-Mouse PLUS	30 100
DUO92002	Duolink In Situ PLA probe anti-Rabbit PLUS	30 100
DUO92003	Duolink In Situ PLA probe anti-Goat PLUS	30 100
PLA Probes MINUS		
DUO92004-30RXN	Duolink In Situ PLA probe anti-Mouse MINUS	30 100
DUO92005-30RXN	Duolink In Situ PLA probe anti-Rabbit MINUS	30 100
DUO92006-30RXN	Duolink In Situ PLA probe anti-Goat MINUS	30 100
Probemaker		
DUO92009-1KT	Duolink In Situ Probemaker PLUS	20 µg
DUO92010-1KT	Duolink In Situ Probemaker MINUS	20 µg
These products are for research use only. 1 reaction is calculated on 40 µL of reagents to cover 1 square cm.		
Detection Reagents Orange		
DUO92007-30RXN	Duolink In Situ Detection Reagents Orange[3]	30 100
Detection Reagents Red		
DUO92008-30RXN	Duolink In Situ Detection Reagents Red[4]	30 100

Cat. No.	Product Description	Size
Detection Reagents Far Red		
DUO92013-30RXN	Duolink In Situ Detection Reagents Far Red[5]	30 100
Detection Reagents Green		
DUO92014-30RXN	Duolink In Situ Detection Reagents Green[6]	30 100
Detection Reagents Brightfield		
DUO92012-30RXN	Duolink In Situ Detection Reagents Brightfield[7]	30 100

[3] Orange – PLA signals detected with the same filters as for Cy3™.
[4] Red – PLA signals detected with the same filters as for Texas Red®.
[5] Far Red – PLA signals detected with the same filters as for Cy5, suitable for Wash Buffer for Fluorescence confocal microscopy.
[6] Green – PLA signals detected with the same filters as for GFP, suitable with red counterstaining e.g. propidium iodide.
[7] Brightfield – PLA signals visualized by enzymatic conversion of HRP/ NovaRED substrate using brightfield microscope..

Accessories		
DUO82047-20L	Duolink In Situ Wash Buffers for Fluorescence	20L
DUO80102-40ML	Duolink In Situ Mounting Medium with DAPI	40ML
DUO82064-1KT	Duolink In Situ Microplate Nuclear Stain and Anti-Fade	1 mL
DUO82065-1EA	Duolink In Situ Microplate Heat Transfer Block	1 block
Software		
DUO90806-1EA	Duolink ImageTool	

Proteins and Peptides

Active Proteins and Peptides Deliver the Bioperformance Your Research Demands

Sigma® Life Science is the leading provider of bioactive proteins and peptides for your cancer research. Our recombinant and natural proteins offer high purity and very low endotoxins, ensuring you get results without risking the effects of undesired contaminants. Highly characterized peptides offer the specificity and purity your research demands, with the convenience of off-the-shelf availability.

More Than 700 New Proteins and Peptides!

- Hormones and Receptors
- Angiogenic factors
- Cancer markers (PSA, CEA)
- Active kinases
- Histone modifying enzymes (HDACs, DNMTs)
- Caspases and substrates

Highlighted New Proteins for Cancer Research

Cat. No.	Protein
SRP2071	Androgen Receptor, Ligand Binding Domain (650-920) Human
SRP2161	Androgen Receptor Human
SRP2085	BCL-10 Human
SRP2080	BRCA1 Human
SRP2087	c-Fos, Proto Oncogene Human
SRP2088	c-Jun, Proto Oncogene Human
SRP2089	c-Myc, Proto Oncogene Human
SRP2163	Estrogen Receptor Human
SRP3031	Endostatin Human
SRP3033	Epiregulin Human
SRP3113	MIA-2 (Melanoma Inhibitory Activity) Human
SRP3125	NOV (Nephroblastoma Overexpressed Gene) Human
SRP3130	Oncostatin M (209 aa) Human
SRP2077	p53 (1-363) C-Terminal Deletion Human
SRP2078	p53 (1-342) C-Terminal Deletion Human
SRP2107	p53 (1-81), wild-type, GST-tagged Human
SRP2108	p53 (1-81), mutant, GST-tagged Human
SRP2079	p300 Human
SRP2090	Rad51 Human
SRP2081	Retinoblastoma Protein Human

To browse new proteins and peptides by area of interest, visit
sigma.com/proteins

Introducing the Bioguarantee for Active Proteins
Plus, our active proteins deliver validated biological activity now backed by the Bioguarantee.

Bioguarantee
Active Proteins

Sigma Life Science is passionate about biology and we know your time and money is precious. The Bioguarantee offers peace of mind with your purchase of any active protein.

Bioguarantee program details - If the protein does not exhibit expected activity in your assay, you can receive a full credit or replacement product by providing experimental results.*

Active proteins covered by the Bioguarantee include hundreds of cytokines, growth factors, PRECISIO® kinases, and more!

For more details, visit
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* Experimental results must be submitted via the Protein Bioguarantee Form within 12 months of the date of purchase. All required fields of the Protein Bioguarantee Form must be completed. Refunds and replacements contingent to claim review by technical service team. Credit covers the cost of protein. Product replacements depend on product availability.

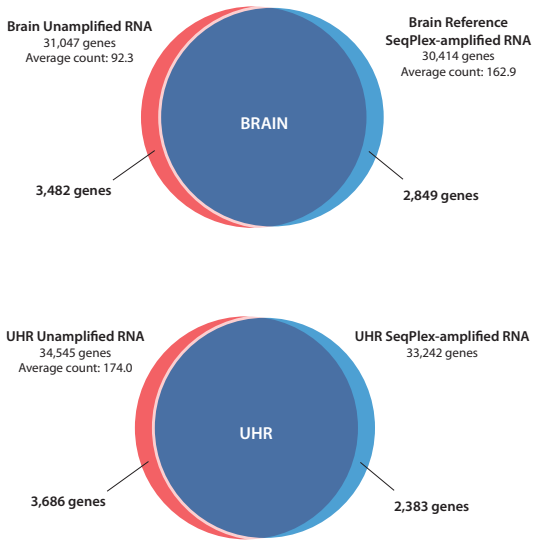
Whole Transcriptome Amplification Sequencing (SEQR)

The SeqPlex RNA Amplification Kit for whole genome transcriptome amplification (WTA) is designed to facilitate next-generation sequencing (NGS) of extremely small quantities of degraded/highly fragmented RNA including non-polyA-tailed RNA. The yields from serum, single cells, RNA immunoprecipitation (RIP), or formalin-fixed paraffin-embedded tissue samples (FFPE) are often less than required for successful NGS library preparation. The SeqPlex kit allows the user to pre-amplify these RNA samples while maintaining patterns of differential expression found in the unamplified sample, prior to entering an NGS workflow.

This kit is an extension of the WTA product line and has been developed to integrate with the Illumina® (GAIIx sequencer), SOLiD™ System (from Life Technologies), Ion Torrent (from Life Technologies), and other next generation sequencing workflows.

	Reads Detected	Aligned Reads	% Aligned Reads	% Primer Removed
Unamplified Brain	31,294,959	30,355,813	97.00%	NA
Unamplified UHR	32,495,951	31,267,174	96.25%	NA
Amplified Brain	31,606,052	26,714,550	84.52%	91.3%
Amplified UHR	31,786,518	26,710,691	84.03%	91.0%

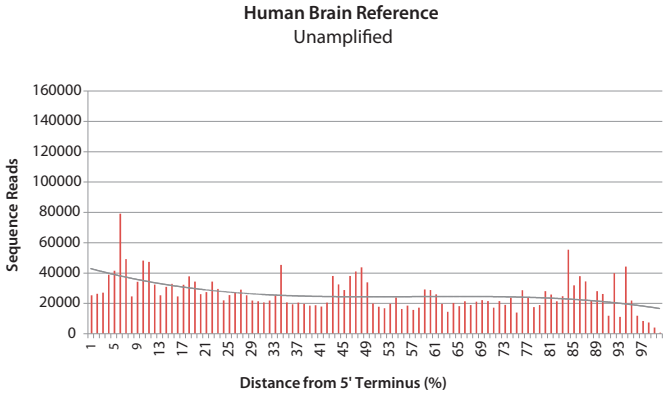
The SeqPlex RNA Amplification kit was used to amplify 2.5 ng of Ambion's Human Brain Reference Total RNA (Brain) and Stratagene's Universal Human Reference RNA (UHR). Deep sequencing was performed with both unamplified and SeqPlex-amplified RNA on an Illumina HiSeq2000. Approximately 84% of reads from SeqPlex-amplified samples align with the human genomic reference compared with 96-97% for unamplified. Results show > 90% of the primer sequences are removed by the SeqPlex primer-removal procedure for both amplified RNA samples. The residual 9% primer sequence accounts for most of the non-aligned reads.

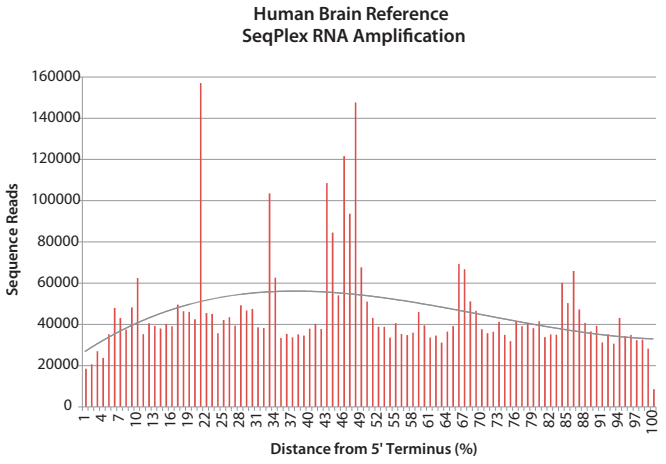


Overlap between genes detected for unamplified and SeqPlex-amplified RNA. Approximately 90% of the aligned reads from SeqPlex-amplified aligned to the same Refseq genes as for unamplified.

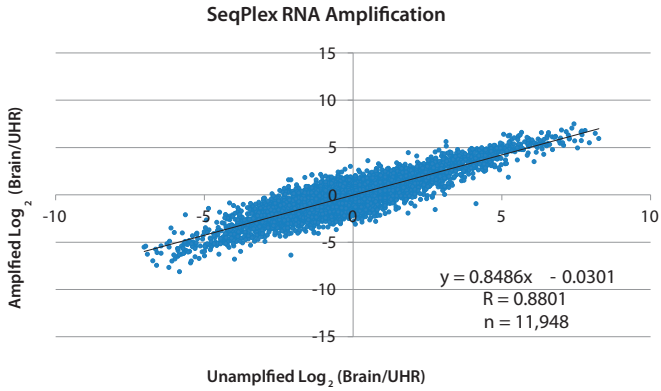
Features and Benefits

- Amplify fragmented or intact RNA from all sources including FFPE and RIP
- Microgram quantities of double-stranded cDNA from picogram quantities of total RNA in approximately 8 hours
- Semi-degenerate + oligo dT library primer mix for more complete uniform amplification and transcriptome coverage and efficient priming
- No need to fragment DNA before sequencing
- Compatible with next generation sequencing workflow platforms (except Pacific Biosciences and Helicos systems)





SeqPlex library synthesis uses semi-degenerate priming plus oligo-dT for cDNA synthesis without 3′ bias. In this plot, the x-axis represents a composite of known Refseq transcripts, with distance from each respective 5′ end described as a per cent of the transcript length. This relative distance from the 5′ end, mapped against the total number of reads in the transcriptome at that position, shows similarly uniform coverage for unamplified and SeqPlex-amplified total RNA



SeqPlex RNA Amplification kit maintains representative transcript levels during amplification. The plot above of amplified versus unamplified differential expression (human brain/UHR) shows a correlation coefficient approaching 0.9, confirming the capability of the SeqPlex RNA amplification kit to perform with minimal bias.

Ordering Information

Cat. No.	Product Description	Size
SEQR	SeqPlex RNA Amplification Kit	SEQR-10RXN SEQR-50RXN SEQR-500RXN (on demand)

For more information, visit
sigma.com/seqr

KiCqStart® Primers for Two-Step and One-Step SYBR® Green I RT-qPCR

Save Time and Money Quantifying Gene Expression with Ready-to-Order, Predesigned Primer Pairs from Sigma® Life Science

Features:

- Easy searching and ordering with Sigma Life Science's state-of-the-art gene search tool
- Available as up to three ranked sets of forward and reverse primer pairs for all available genes from common model organisms
- One oligonucleotide per tube for maximum experimental flexibility

Design Characteristics		Oligo Characteristics	
GC Content	40 – 60%*	Molecule	DNA (all sequences are verified by mass spec QC) No modifications
Melting Temperature	55.0 ± 5 °C	Contents	1 forward and 1 reverse primer
Secondary Structure	None	Length	18 – 24 bases*
3' Clamping	Minimal	Purification	RP cartridge
Homology	None	Format	3 OD minimum yield, dry

*95% of primer pairs fall within these specifications.

KiCqStart® SYBR® Green qPCR ReadyMix™

Sigma Life Science is proud to present KiCqStart SYBR Green ReadyMixes for fast qPCR. Each mix is a ready-to-use 2X concentration with all the necessary reagents; just add your primers and template. The optimized formulation includes SYBR Green I dye, an antibody-mediated Hot-Start Taq DNA polymerase, dNTPs, $MgCl_2$, and proprietary buffers and stabilizers. These new mixes also incorporate the optimal concentration of ROX™ passive reference dye, depending on which real-time PCR instrument is being used.

KiCqStart Your qPCR Assays Today!

- **Speed** – assay results in as little as 33 minutes
- **Quality** – highly efficient and sensitive real-time PCR results
- **Ease of use** – little to no optimization required

Cat. No.	Product Description	Quantity*
KCQS00	KiCqStart SYBR Green qPCR ReadyMix	250 reactions 1250 reactions 5000 reactions
KCQS01	KiCqStart SYBR Green qPCR ReadyMix, Low ROX	250 reactions 1250 reactions 5000 reactions
KCQS02	KiCqStart SYBR Green qPCR ReadyMix with ROX	250 reactions 1250 reactions 5000 reactions
KCQS03	KiCqStart SYBR Green qPCR ReadyMix, iQ	250 reactions 1250 reactions 5000 reactions

*Number of reactions based a 20 µL volume

Benefits:

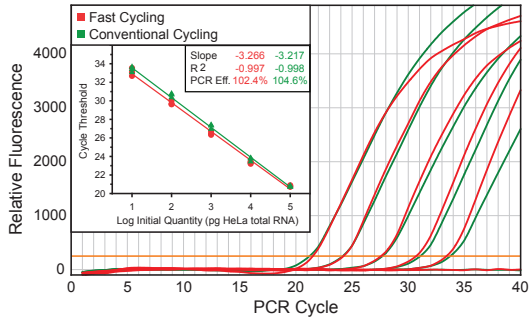
- Developed with sophisticated bioinformatics tools and validated *in silico* to avoid off-target amplification
- MIQE compliant – sequences are provided at the time of shipment
- Compatible with any thermal cycler

	From Scratch	KiCqStart Primers
Target analysis done	x	✓
Design characteristics set	x	✓
Oligo characteristics set	x	✓
Easy to order	x	✓

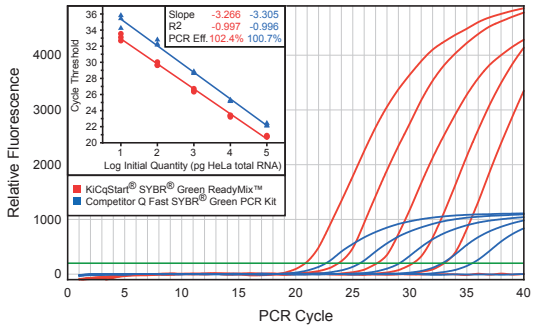
Maximize Performance:

Get the most out of your KiCqStart Primers by using Sigma's ReadyScript® cDNA Synthesis Mix (**Product No. RDRT**) and KiCqStart SYBR Green qPCR ReadyMix™ (**Product No.** KCQS00) for two-step reactions.

To learn more or order, visit
sigma.com/ksprimers



Fast-cycling KiCqStart SYBR Green qPCR ReadyMix demonstrates equal performance to conventional SYBR Green protocol and reagents.



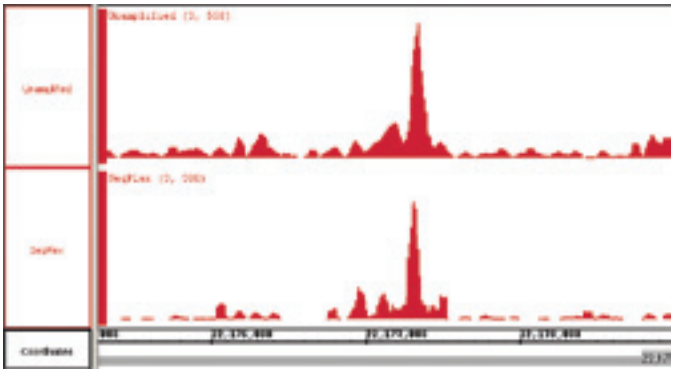
Target gene was amplified from log-fold dilutions of total HeLa cell cDNA (100 ng to 10 pg) using KiCqStart SYBR Green qPCR ReadyMix or Competitor Q according to each manufacturer's protocol. Plots represent averages of quadruplicate reactions.

SeqPlex DNA Amplification Kit

Suitable For Use With Next Generation Sequencing Technologies

The SeqPlex DNA Amplification Kit for whole genome amplification (WGA) is designed to facilitate next-generation sequencing (NGS) from extremely small quantities or from degraded/highly fragmented DNA. The yields from chromatin immunoprecipitation (ChIP) or formalin-fixed paraffin-embedded tissue samples (FFPE) are often less than required for successful NGS library preparation. The SeqPlex kit allows the user to pre-amplify these and other small quantity/highly fragmented DNA samples for input into a NGS workflow.

This kit is an extension of the WGA product line and has been developed to integrate into the Illumina® (GAIIx sequencer), SOLiD™ System (from Life Technologies), Ion Torrent (from Life Technologies) and other next generation sequencing workflows, as a DNA amplification technology.



SeqPlex DNA Amplification (SEQX) was performed on 100 picograms of ChIP DNA from a pool prepared using Imprint® Chromatin IP kit (CHP2) and 4.32 micrograms of H1.4K26me2. Approximately 150 ng of SeqPlex product or original ChIP DNA were submitted for Illumina sequencing. SeqPlex (bottom) and Unamplified (top) show similar sequence alignment. Reads are visualized using Integrated Genome Browser 6.5.3.

Ordering Information

Cat. No.	Product Description	Quantity
SEQX	SeqPlex DNA Amplification Kit	10RXN 50RXN 500RXN

Features and Benefits

- Compatible with next generation sequencing platforms
- Patent pending random priming technology amplifies fragmented or intact DNA (obtained by ChIP or any other protocol)
- Provides highly uniform amplification across the entire genome with minimal sequence bias
- Directly compatible with validated sequencing library preparation protocols on existing NGS platforms
- Enhanced primer design for more complete genomic coverage

For more information, visit
sigma.com/wga

MISSION® Inducible shRNA

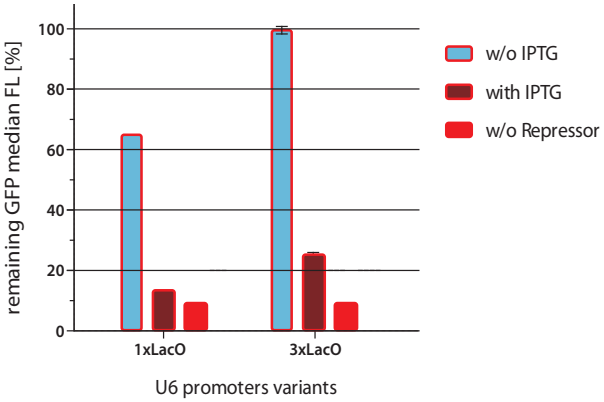
Get the Entire MISSION shRNA Library in an IPTG-Inducible Vector

Why Use IPTG-Inducible shRNA?

- Temporally-controlled gene silencing useful for lethal gene knockdown
- Proven to work *in vivo* and *in vitro*
- Single vector system for effective inducible knockdown
- Fast response time of IPTG induction
- Tight regulation and high induction of shRNA expression
- Available in the widely used TRC vector backbone
- Lentiviral delivery increases the number of targetable cell lines
- Developed at the Broad Institute by the TRC

Customize Your Inducible shRNA

- Vector: 1x LacO and 3x LacO
- Titer: $1x10^6$ – $1x10^9$ TU/mL
- Volume: 200 µL – 10 mL
- Choose any TRC clone or Custom Sequence



Comparison of inducible shRNA expression from different U6 promoters.

Jurkat cells with stable GFP expression were infected with different vectors carrying an shRNA against GFP with and without repressor. All the cells were treated with 1 mM IPTG. The remaining GFP fluorescence was compared after 5 days. Cells infected with the empty vector control were used as a negative control. Values represent the mean and standard deviation of three independent experiments.

Dial Into the Latest Development from the RNAi Consortium (TRC)

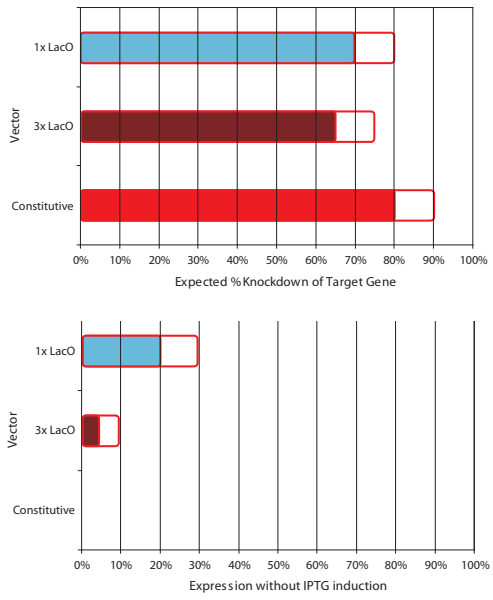
Constitutively expressed shRNAs are useful for most RNAi needs, but further characterization often requires the ability to tune gene expression. Regulating expression is especially important when studying essential and lethal genes. Sigma® Life Science now offers IPTG-inducible vectors as the latest development from our continued partnership with the TRC. Trust in MISSION Custom Services to create the perfect clone to fit your research.

Cat. No.	Product Description
SHC314V	MISSION 1x LacO Inducible TurboGFP™ shRNA Control Transduction Particles
SHC334V	MISSION 3x LacO Inducible TurboGFP™ shRNA Control Transduction Particles
SHC317V	MISSION 1x LacO Inducible Luciferase shRNA Control Transduction Particles
SHC337V	MISSION 3x LacO Inducible Luciferase shRNA Control Transduction Particles
SHC312V	MISSION 1x LacO Inducible Non-Target shRNA Control Transduction Particles
SHC332V	MISSION 3x LacO Inducible Non-Target shRNA Control Transduction Particles

IPTG-inducible RNAi

The pLKO vector has been redesigned to contain LacI (repressor) and a modified human U6 shRNA promoter with LacO (operator). In the absence of IPTG (isopropyl-β-D-thiogalactoside), an analog of lactose, the LacI repressor binds the LacO operator preventing expression of the shRNA. When IPTG is added, the allosteric LacI repressor changes conformation allowing expression from the modified U6 promoter.

Gene Slicing Potency



Inducible vs. Constitutive Vector Performance

The data demonstrate the performance of the 1xLacO and 3xLacO vectors in comparison to an equivalent constitutive design. Choose the vector that will work best for your application.

For more information, visit
sigma.com/inducible

MISSION® microRNA Mimics, Inhibitors, and siRNA

MISSION miRNA Mimics are designed to enter the miRNA pathway and mimic mature miRNA. This enables researchers to confidently analyze miRNA function. MISSION miRNA Mimics utilize a unique design and modification that reduces off-target effects.

miRNA Mimics are available in a ready-to-use miRBase version 17 library, or select from more than1,900 individual mimics. **Custom Mimics for all species are available, including the current miRBase version content. Please inquire.**

MISSION miRNA Mimics

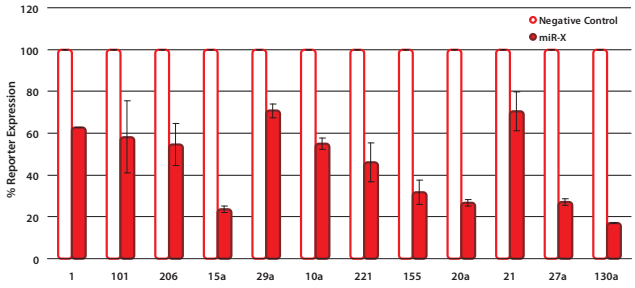
- Functionally tested for knockdown efficiency
- >1,900 miRNA Mimics
- Quick delivery, ships within 2 business days

Human miRNA Mimic miRBase Version 17 Library

The library includes 1,902 miRNA Mimics prepared in a convenient 96-well format. The two outside columns of each plate are empty for the addition of controls. Each miRNA Mimic is provided at 0.25 nmole/well and 2 non-targeting miRNA controls are included on each plate.

Cat. No.	Description
HMI0001-1920	Individual miRNA Mimics (5 nmole)
MI00200	miRNA Mimic library (0.25 nmole)
HMC0002-0003	Negative controls (5 nmole)
Inquire	Custom miRNA Mimic (10 nmole)

MISSION miRNA Mimics significantly reduce known gene target expression



HeLa cells were co-transfected with MISSION miRNA Mimics and psi-CHECK2 Dual Luciferase Reporter Construct (Promega), containing corresponding miRNA target sequences. Constructs contained full length 3'UTR sequence-specific miRNA sequences (100% complementary to the mature miRNA). The MISSION miRNA Mimic negative controls are non-human miRNAs, predicted to not target the human genome/transcriptome.

How to Order

To place an order, or learn more about our miRNA product offering, visit
sigma.com/mimics

MISSION Synthetic miRNA Inhibitors

Small, double-stranded RNA molecules designed to inhibit a specific mature miRNA. The miRNA inhibitors were designed using the mature miRNA sequence information from miRBase and are 2'-O-methylated RNA duplexes with a miRNA binding site on each strand. Optimal miRNA inhibition is provided after transfection due to the robust secondary structure of the inhibitor.

- >2,000 human and >1,300 mouse inhibitors
- Custom synthesis available for a variety of species

Cat. No.	Description	Quantity
HSTUDxxxx	Individual human miRNA inhibitor	5 nmole
MSTUDxxxx	Individual mouse miRNA inhibitor	5 nmole
NCSTUD001-002	Negative controls	5 nmole
Inquire	Custom miRNA inhibitor	20 nmole

*Quantity provided is sufficient to bind the indicated amount of target miRNA.

How to Order

To place an order or learn more about our synthetic miRNA inhibitors, visit
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MISSION siRNA

- Pre-designed and Custom siRNA
  - Designed using the Rosetta Design Algorithm to provide the most effective and specific siRNA sequences for your target gene
- iScale/ *In vivo* siRNA
  - Intermediate to large scale siRNA with a variety of modifications for *in vitro* and *in vivo* use
- siRNA Libraries/ Panels
  - Human, mouse, and rat species available with 3 siRNA provided per gene
- Positive and Negative Controls
  - Simplify transfection optimization
- N-TER™
  - siRNA peptide transfection system for difficult to transfect cells

How to Order

To place an order or learn more about our siRNA product offering, visit
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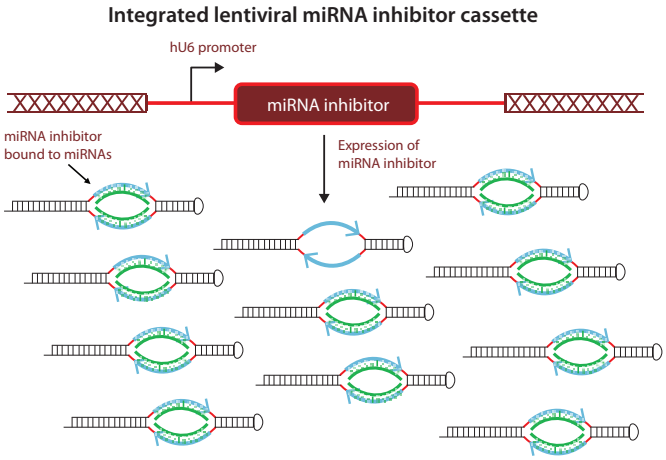
Elucidate miRNA Function with MISSION® Lenti microRNA Inhibitors

MicroRNA Inhibition in a Lentiviral Plasmid Vector

Inhibition of microRNAs is essential to studying their function. Sigma® Life Science offers a collection of individual microRNA inhibitors which are designed using a proprietary algorithm based upon the tough decoy (TuD) design.[1] Each miRNA inhibitor construct has been cloned and sequence verified to ensure a match to the target miRNA.

Lenti miRNA Inhibitor Design



Lentiviral miRNA Inhibitor Expression Regulates miRNA Function

Expression of the miRNA inhibitor is driven by the hU6 promoter upon genomic integration of the lentiviral transfer vector into the host cell post-transduction. miRNA inhibitors are able to competitively bind specific miRNAs and prevent them from regulating their endogenous targets.

Reference:
1. Haraguchi, T., et al., Vectors expressing efficient RNA decoys achieve the long-term suppression of specific microRNA activity in mammalian cells. Nucleic Acids Res., 37, (**2009**).

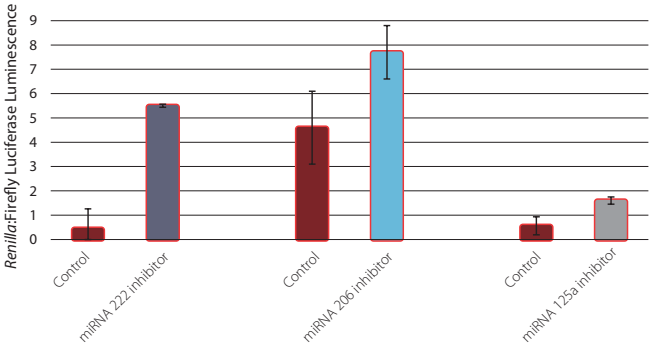
Benefits of Lenti miRNA Inhibitors

- Allows for potent inhibition of desired miRNA
- Lentiviral format allows for efficient delivery of the inhibitor into a wide variety of cell types
- Enables long-term inhibition without repeat transfections

Ordering Information	
Cat. No.	Product Description
HLTUD0001-HLTUD2235	MISSION Lenti microRNA Inhibitor, Human
MLTUD0001-MLTUD1405	MISSION Lenti microRNA Inhibitor, Mouse
HLTUD001C	MISSION Lenti microRNA Inhibitor, *Arabidopsis thaliana* Control
HLTUD002C	MISSION Lenti microRNA Inhibitor, *Caenorhabditis elegans* Control
CSTTUD	MISSION Custom Lenti microRNA Inhibitor

To learn more about our lenti miRNA inhibitors, visit
sigma.com/lentiinhibitor

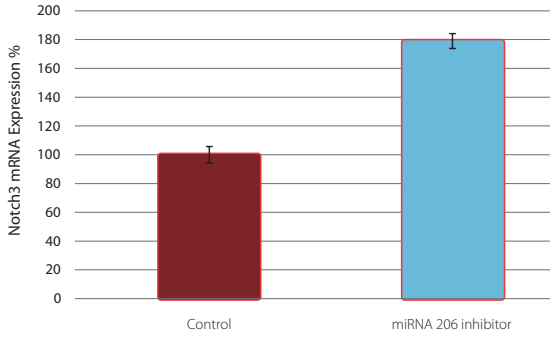
Validation of Lenti miRNA Inhibitors by Dual Luciferase Assay



Dual Luciferase Assay: HeLa Lenti miRNA Inhibitor Cell Lines

HeLa cells were stably transduced with lentivirus harboring the miRNA inhibitors indicated. Stable pools were cultured for a minimum of two weeks, and were then transfected with dual luciferase reporter constructs corresponding to the miRNA of interest. Ratios of renilla:firefly luciferase luminescence were calculated for each cell line tested, and compared to control inhibitor cells. An increase in *Renilla*:firefly luminescence in inhibitor-expressing cells relative to controls cells indicates functionality of the inhibitor.

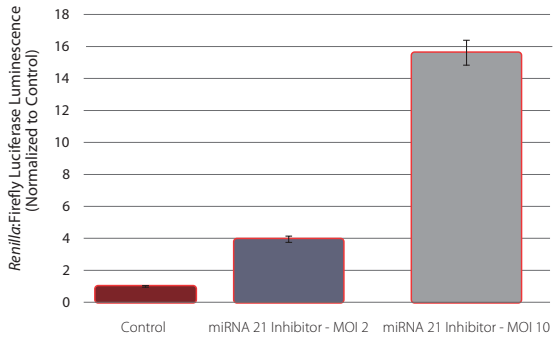
Inhibition of miR-206 Upregulates Notch3 Expression



qRT-PCR of Notch3 in HeLa Lenti miRNA Inhibitor Cell Lines

miR-206 has been shown to regulate the expression of Notch3 in HeLa cells. To confirm the miR-206 inhibitor can alter the actions of miR-206 with respect to its endogenous downstream targets, qRT-PCR was performed on total RNA preparations from HeLa cells stably expressing either the miR-206 inhibitor or control inhibitor. Expression of Notch3 increased by 78% relative to control cells, indicating efficient inhibition of miR-206 in this cell line.

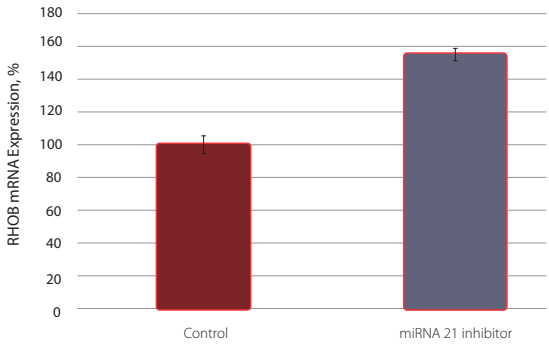
Higher MOI may Increase miRNA Inhibition



Dual Luciferase Assay for miR-21 in HepG2 Cells

Increased multiplicity of infection (MOI) can be used to increase miRNA inhibition. HepG2 cells were stably transduced with control Lenti miRNA inhibitor or miR-21inhibitor at varied MOI. Stable pools were transfected with the dual luciferase reporter vector for miR-21, and luciferase ratios were calculated accordingly. Results indicate an increased MOI of Lenti inhibitor can be used to increase inhibition of a specific miRNA, as the *Renilla*:firefly luminescence increases with higher MOI.

Inhibition of miR-21 Upregulates RHOB Expression



qRT-PCR of RHOB in HepG2 Lenti miRNA Inhibitor Cell Lines

miR-21 has been shown to regulate the expression of RHOB in hepatocytes. To further validate the miR-21 inhibitor, qRT-PCR was performed on total RNA preparations from Hep G2 cells stably expressing either the miR-21 inhibitor or control inhibitor. Expression of RHOB increased by 55% relative to control cells, indicating efficient inhibition of miR-21 in this cell line. Nearly identical results were obtained for this same target and inhibitor combination in HeLa cells (data not shown).

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