MERCK

MISSION™ CRISPR Genome Editing

The life science business of Merck operates as MilliporeSigma in the U.S. and Canada.

Sigma-Aldrich®

Lab & Production Materials

We are dedicated to supporting you and all of your breakthroughs by providing an unmatched genome editing products and services portfolio. As the first company to offer custom biomolecules to help researchers understand gene function, we are committed to innovation in the field. From exploratory gene function experiments, to therapeutic applications, we are your partner.

Table of Contents

design. engineer. innovate.

Edit with confidence using MISSION™ genome editing reagents. Our R&D is committed to developing and supplying innovative technologies for genome editing and functional genomics, including CRISPR, ZFN, and RNAi products, to cover your entire work flow.

Gene Editing for Every Lab

The simplicity and speed of the MISSION™ CRISPR system enables gene editing to be a tool for every research lab. Design guide RNAs (gRNAs) to target any gene in any species. Rely on our proprietary bioinformatics algorithm to reduce off-target risk and guarantee activity.

Features of the MISSION™ CRISPR/Cas9 System

Innovative, High-Quality CRISPR Reagents from the Genome Editing Experts

- Ready-to-use CRISPR products with your gRNA already cloned into the vector of interest
- Codon-optimized *S. pyogenes* Cas9, Cas9-D10A nickase, enhanced specificity eSpCas9, and GFP labeled Cas9 available as protein or plasmid

Best In-Class Bioinformatics for gRNA Designs

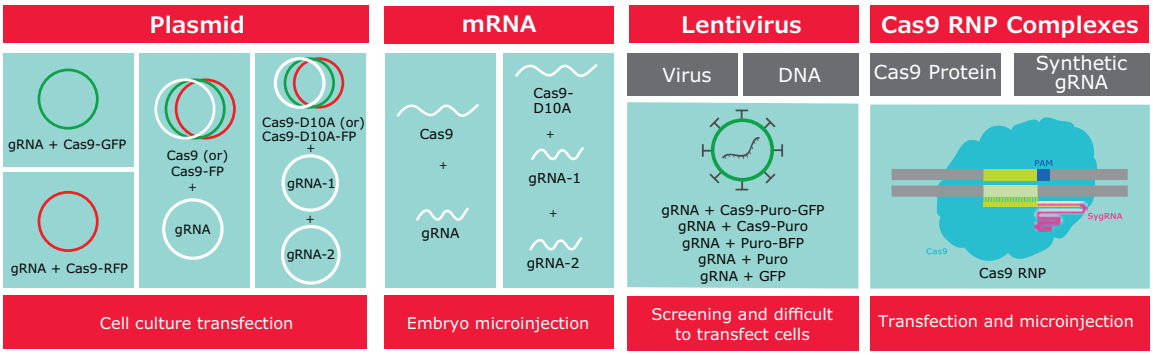
- Unique gRNAs designed by our world-class bioinformatics team to minimize off-targeting
- Standard guide sequences have at least 3 bp of mismatch to all other sites in the genome
- Stringency may be modified for complex projects

Convenient online ordering available

Visit **SigmaAldrich.com/OrderCRISPR** to:

- Screen human and mouse genes with Sanger QuickPick™ Lentiviral KnockOut gRNAs
- Target any human or mouse gene with our Guaranteed* Predesigned gRNAs
- Upload your own gRNA sequence for synthesis in any format
- Design your own CRISPR gRNAs with our interactive, online bioinformatics webtool at **SigmaAldrich.com/CRISPRdesign**
- Custom gRNA designs are available to introduce specific sequence changes made through homology directed repair (HDR) including SNP variants/point mutations, fused reporter genes, restriction sites and LoxP sequences

CRISPR PRODUCT FORMATS



*We guarantee the performance of all predesigned MISSION™ SygRNA® gRNAs. If your MISSION™ predesigned synthetic guide RNAs do not yield detectable cleavage at the intended target site, we will provide you a one-time replacement, free of charge.

To qualify for this guarantee, please send an image or sequencing data from a single experiment demonstrating detectable cleavage using one of our available positive controls, side-by-side with the negative results from your predesigned MISSION™ SygRNA® CRISPR. To receive your replacement, visit **SigmaAldrich.com/AskaScientist** and include sample data from a representative experiment (T7E1, TIDE, or NGS), specifying the MISSION™ gRNA ID used.

CRISPR-Cas9 Plasmid Reagents

- Sanger QuickPick™ KnockOut clones, ideal for screening
- Easy-to-use all-in-one CRISPR plasmid with GFP or RFP for enrichment of transfected cells
- Flexible dual plasmid system that expresses gRNA and Cas9 separately
- CRISPR paired nickase for increased specificity
- Lentiviral CRISPR for screening and hard-to-transfect cells

All-in-One CRISPR plasmid

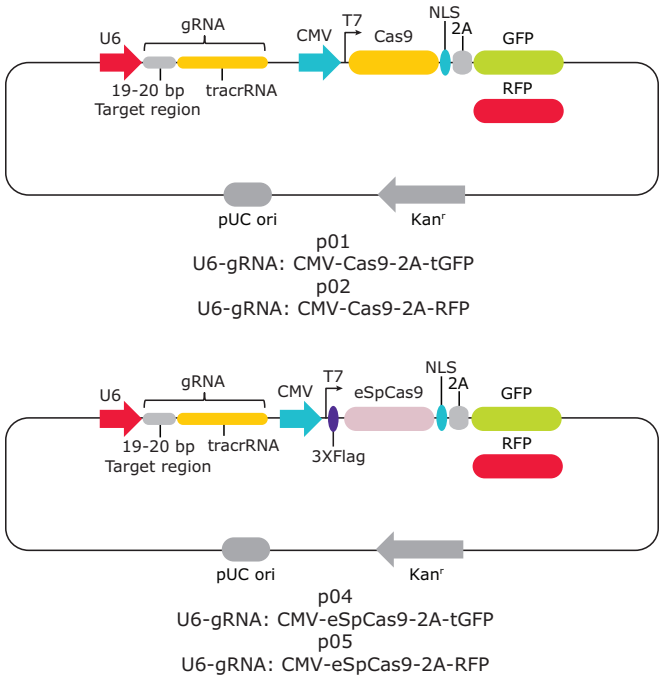
- Efficiently deliver gRNA, Cas9, and fluorophore with a convenient single plasmid, see **Figure 1**
- Co-express GFP or RFP with WT SpCas9 or eSpCas9
- *In vitro* transcribe Cas9 mRNA from the T7 promoter

Dual Vector CRISPR gRNA and Cas9 plasmids

- Flexible dual vector system that expresses gRNA and Cas9 separately (**Figure 2**)
- Cas9 plasmids that co-express GFP or RFP are available
- For easy to transfect cells, may increase Cas9 cutting efficiency
- Independent gRNA expression increases versatility (pair gRNA with a variety of Cas9 formats or directly introduce in stably expressed Cas9 cell lines)

Figure 1.

All-in-one MISSION™ CRISPR vectors with U6-gRNA and CMV-Cas9 co-expressed with GFP or RFP.



For details about all CRISPR plasmid vectors, visit
SigmaAldrich.com/CRISPRessentials

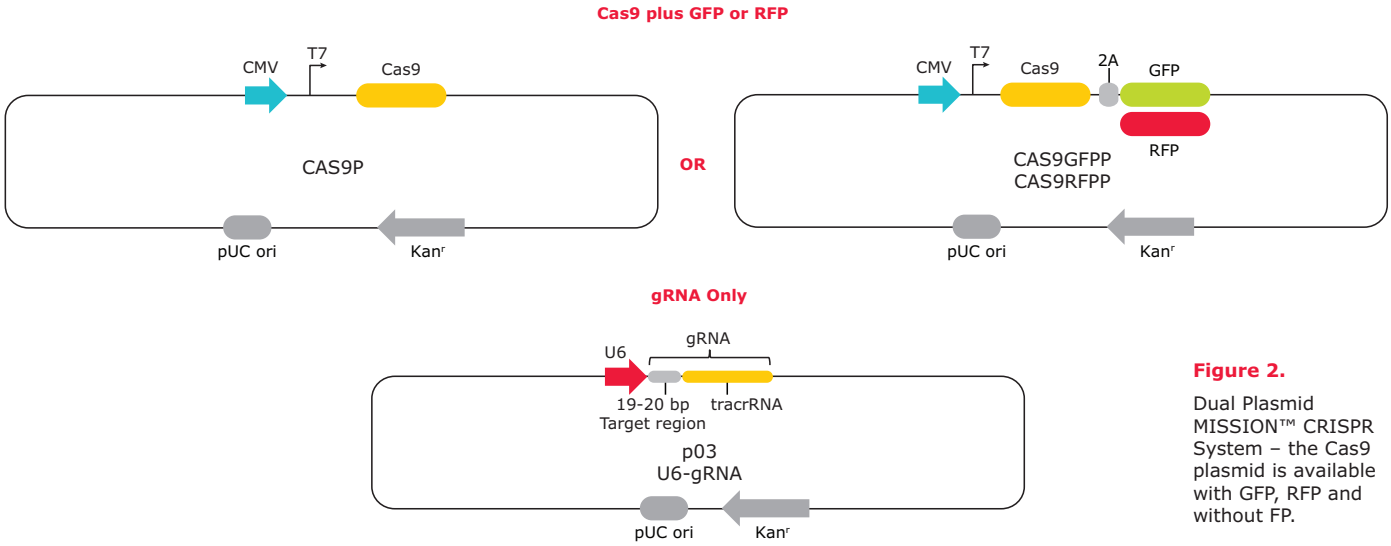


Figure 2.

Dual Plasmid MISSION™ CRISPR System – the Cas9 plasmid is available with GFP, RFP and without FP.

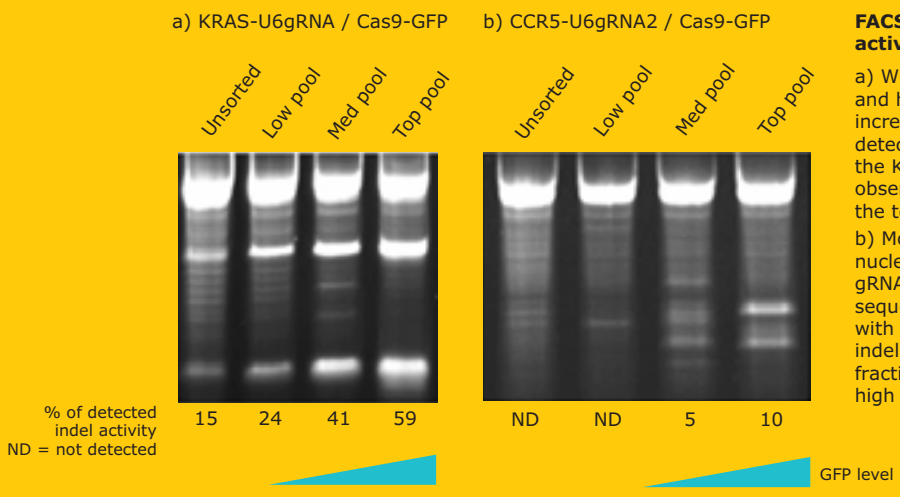
Table 1. Product Listing

Cat. No.	Description	Qty.
CAS9P-1EA	Cas9 plasmid	1 µg
CAS9GFPP-1EA	Cas9-2A-GFP plasmid	1 µg
CAS9RFPP-1EA	Cas9-2A-RFP plasmid	1 µg
CRISPR	Custom gRNA plasmid	1 µg std.

For more lentiviral plasmid vectors, reference page 13.

small but Mighty

Some cell types and/or genomic locations are more difficult to target than others. Using the MISSION™ All-in-One CRISPR vector system, co-expression of Cas9 and GFP (or RFP) from the same plasmid creates the possibility of enriching cell populations for desired genome modification via fluorescence activated cell sorting (FACS). FACS enrichment can significantly reduce the labor and cost associated with cloning and genotyping.



FACS enrichment correlates to increased indel activity detection

a) When cell fractions were divided into low, medium, and high pools based on GFP expression, corresponding increases in indel activity, identified by a mismatch detection assay, were observed. For a gRNA targeting the KRAS locus, a 4-fold increase in indel activity was observed when comparing the unsorted population vs. the top 2% of GFP-expressing cells.

b) Most gRNAs produce detectable indel activity in initial nuclease screens against gene targets, but current gRNA design rules fail to predict activity based on sequence content or genomic context. Cells targeted with CCR5 gRNA initially failed to produce detectable indels. Following sorting into low, medium, and high GFP fractions, indel activity was detected in the medium and high GFP fractions.

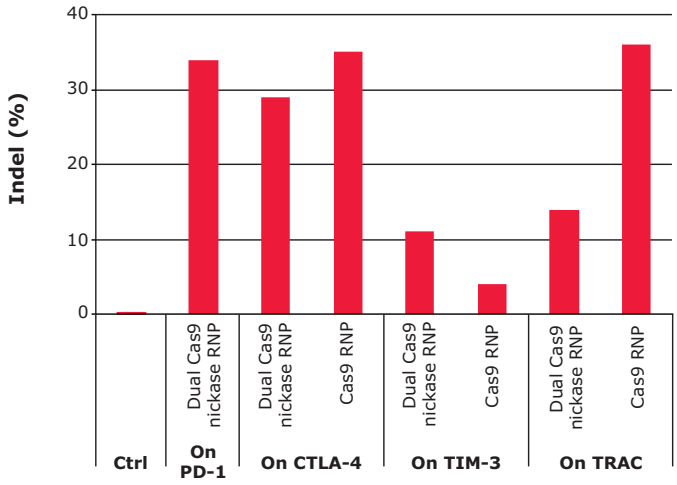
CRISPR Nickase Reagents

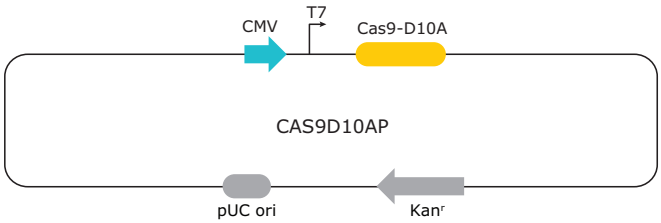
Increase Specificity with MISSION™ CRISPR Paired Nickases

- Cas9-D10A nicking nuclease in conjunction with paired gRNAs potentially reduces off-target activity by expanding the CRISPR DNA sequence recognition tract to lengths similar to those for ZFNs
- CRISPR paired nickase gRNAs target virtually any region of any species
- The gRNAs for paired nickases are available either as:
  - two synthetic crRNAs to be used with synthetic tracrRNA
  - two synthetic single guide RNAs (sgRNA)
  - two separate, ready-to-use, transfection-grade gRNA plasmids
  - two separate, *in vitro* transcribed gRNAs
- The Cas9-D10A nicking nuclease must be purchased separately as plasmid, mRNA, or protein

Figure 3.

Genome editing on PD-1, CTLA-4, TIM-3, TRAC in **Human Primary T Cells** with Dual Cas9_Nickase RNPs (Cas9_nickase proteins + paired mod-sgRNAs) or Cas9 RNPs (Cas9 protein + mod-sgRNA). Indels were measured by TIDE assay.





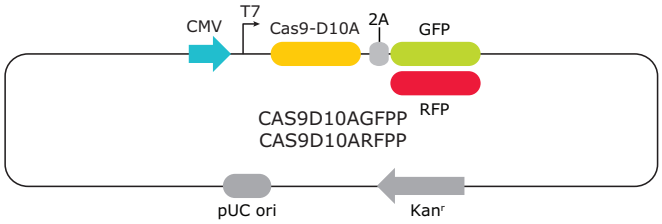


Figure 4.

Plasmid maps for the Cas9-D10A nickase and the U6-gRNA vectors. Cas9-D10A nickase-only plasmid is also available with GFP or RFP.

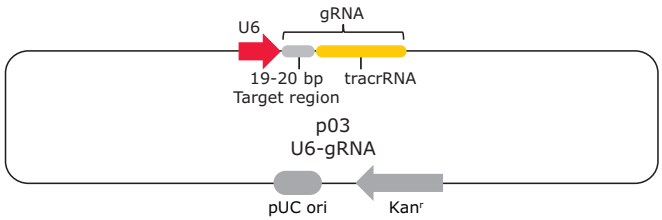


Figure 5.

To optimize paired nickase functionality, gRNAs are designed in a PAM-out orientation (5'-5'), with PAM spacing between 30 and 150 bp.

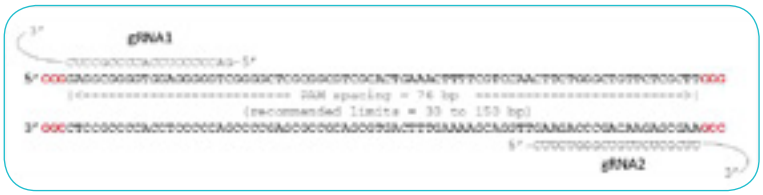


Table 2. Product Listings

Cat. No.	Description	Amount	Additional Details
CAS9D10AP-1EA	CRISPR Cas9-D10A Nickase Plasmid	1 µg	Concentration: 20 ng/µL
CAS9D10AGFPP-1EA	CMV-Cas9-D10A-2A-GFP Plasmid	1 µg	Concentration: 20 ng/µL
CAS9D10ARFPP-1EA	CMV-Cas9-D10A-2A-RFP Plasmid	1 µg	Concentration: 20 ng/µL
CAS9D10AMRNA-1EA	CRISPR Cas9-D10A Nickase mRNA	25 µg	Concentration: 500 ng/µL
CAS9D10APR-50UG **CAS9D10APR-250UG**	Cas9-D10A Nickase Protein	50 µg 250 µg	Amount: ≥ 300 pmol Amount: ≥ 1500 pmol
CRISPR	Custom gRNA, Plasmid DNA	1 µg std	Additional amounts available: 10 µg, 25 µg, and 100 µg
CRISPR	Custom gRNA, purified IVT RNA	4 µg std	Concentration: 200 ng/µL
CRISPR	Custom Synthetic single guide RNA, sgRNA (crRNA:tracrRNA in one)	3 nmol	• Purification: HPLC • Stabilizing and custom modifications available
CRISPR	Custom Synthetic CRISPR RNA, crRNA (tracrRNA sold separately)	2 or 5 nmol	• Purification: Desalt or HPLC available • Stabilizing and custom modifications available on HPLC-purified crRNA • Requires tracrRNA with same modifications as crRNA
TRACRRNA05N-5NMOL	SygRNA® *Sp*Cas9 tracrRNA	5 nmol	• HPLC-purified • For use with crRNA Desalt or HPLC-purified. • If using crRNA with stabilizing modifications, choose TRACRRNAMOD
TRACRRNAMOD-5NMOL	SygRNA® *Sp*Cas9 Modified tracrRNA	5 nmol	• HPLC-purified • For use with crRNA stabilizing modifications

For more information, visit
SigmaAldrich.com/CRISPRessentials

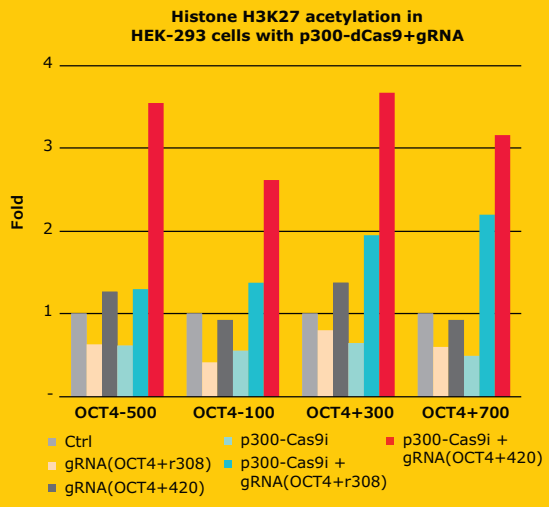
CRISPR Epigenetic Activator

The Scientist Top 10 Innovation Award recognized the dCas9-p300 Epigenetic Activator system as an advancement to human health, enabling new platforms for drug screening, gene therapy and disease monitoring.

The dCas9-p300 turns on a target gene by acetylating a specific histone, thus relaxing the chromatin structure and activating transcription. In this way, the researcher can up-regulate expression of a gene in its native chromosomal context rather than adding exogenous cDNA driven by a foreign promoter.

dCas9-p300 activates endogenous gene expression at high levels using a single gRNA, offering innovative activation-based genome wide screening.

Cat. No.	Description	Qty.
DCAS9P300-1EA	Sigma-Aldrich® CRISPR dCas9-p300 Activator Expression Plasmid	1 ug
CRISPR17-1EA	CRISPR Activator Human Oct4 Positive Control Plasmid	1 ug
CRISPR	Custom CRISPR Products	1 ug std.



p300-dCas9 induced targeted histone acetylation

CRISPR RNA

Injection-Ready *In Vitro* Transcribed (IVT) RNA

- Ready-to-use purified gRNAs for microinjection or cell culture
- Designed using stringent bioinformatics rules to minimize potential off-target effects
- Ideal for researchers creating transgenic animal models or any research requiring a short interval of CRISPR expression
- Eliminates promoter compatibility concerns enabling expression in most cell types and organisms
- Purchase wild-type Cas9 or Cas9-D10A nucleases separately

Table 3. CRISPR products in RNA format

Cat. No.	Description	Qty.
CAS9MRNA	Cas9 mRNA	25 µg
CAS9D10AMRNA	CRISPR Cas9-D10A Nickase mRNA	25 µg
CRISPR	Purified IVT guide RNA	4 µg

value in validation

Validated gRNA for human, mouse, or rat targets save time and money at the bench. Our expert team of scientists verifies cleavage efficiency of a select panel of target-specific gRNA in a model cell line. They identify the best performing gRNA for optimal genome editing results and manufacture to the desired quality specifications.

Do you wish to introduce unique DNA sequences such as point mutations, reporter genes, and LoxP cassettes? Validation packages include Sigma-Aldrich® donor design services and synthesis of donor oligos.

Validation packages include:

- Cas9 plasmid or injection-ready mRNA
- Validated gRNA supplied in synthetic, DNA, or IVT RNA formats
- Validated mismatch detection assay primer sequences
- Standard 120nt donor oligo design and synthesis*

*Customized oligo and plasmid donors available for an additional fee.

Benefits:

- Obtain the best-performing CRISPR for your target
- Save time at the bench using validated reagents
- Rely on our gene editing expertise to optimize project design from start to finish

SygRNA® Synthetic Guide RNA

The SygRNA® synthetic guide RNA system accelerates genome editing with Cas9 protein, mRNA or an established Cas9-expressing cell line. SygRNA® is compatible with a variety of delivery methods including microinjection, lipofection and electroporation.

Selected Applications

- Engineer transgenic animals
- Model disease states in immortalized cells
- Create isogenic iPS cell lines

Advantages

- Fast delivery time – Chemically synthesized crRNA and tracrRNA are manufactured and shipped within 3-5 business days; one-part sgRNAs ship in 7-10
- Ready-to-use – Inject or transfect upon delivery
- Customizable – Any custom sequence or quantity available
- Versatile – Target any sequence in any species

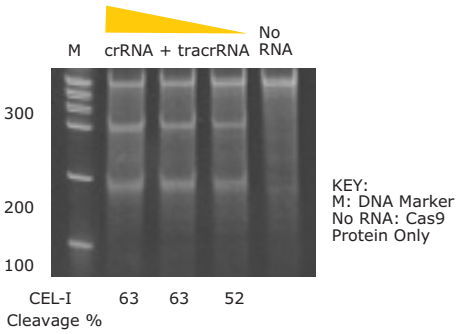


Figure 6.

Cleavage rates of SygRNA® crRNA and tracrRNA with Cas9 protein

Complexes of synthetic crRNA, tracrRNA, and Cas9 protein targeting AAVS1 were delivered by nucleofection (Lonza) into K562 cells. The CEL-I endonuclease assay demonstrates that increased quantity of synthetic crRNA and tracrRNAs improves cleavage efficiency. All lanes represent 5 µg Cas9 protein delivered.

gRNA format	Two-part system		One-part system
	SygRNA® crRNA:tracrRNA	SygRNA® modified crRNA:tracrRNA	SygRNA® modified sgRNA
Structure			
Cost	+	++	+++
Efficiency	++	+++	++++

Table 4. SygRNA® Synthetic CRISPR Configurable Options

Specification	crRNA - two part guide RNA system		sgRNA - one part gRNA system	
Cas9 Species	*Sp*Cas9	*Fn*Cas9†	*Sp*Cas9	*Fn*Cas9†
TracrRNA	Unmodified *Sp*Cas9 crRNA requires TRACRRNA05N	Unmodified *Fn*Cas9 crRNA requires FNCAS9TRACR	Separate tracrRNA sequence not required as single guide/ one-part system incorporates all relevant components of the guideRNA	
	Modified SpCas9 crRNA requires TRACRRNAMOD	Modified crRNA requires Modified FnCas9 tracrRNA (available via Custom crRNA Custom Request)		
Synthesis Scale	2 or 5 nmol		3 nmol	
Purification	Desalt or HPLC		HPLC only	
Modification Option*	Available for HPLC purification only		Available	
TAT	3-5 business days		10 business days	
Recommended Applications	*in vitro* and *in vivo* gene editing		*in vitro* and *in vivo* gene editing	

*2′ O-methyl and phosphothioate modifications can be incorporated to enhance the stability and performance of the synthetic RNA
†FnCas9 should only be used for non-cellular, synthetic applications

Learn more about SygRNA® by visiting
SigmaAldrich.com/SygRNA

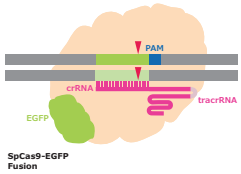
Cas9 Proteins

Purified recombinant Cas9 protein shortens the experimental timeline from delivery to expression by bypassing translation. The lyophilized Cas9 protein is quickly reconstituted and complexes with a variety of gRNA formats.

CRISPR Cas9 Proteins

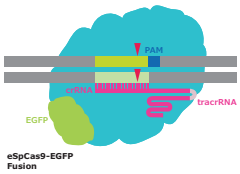
SpCas9-EGFP Fusion

Original Wild-Type Cas9 fused to enhanced green fluorescent protein. Ideal for flow cytometry applications and visualization of transfected RNP complexes. Highly efficient.



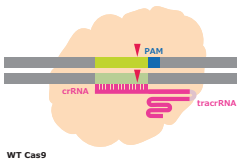
eSpCas9-EGFP Fusion

Cas9 variant with improved specificity fused to enhanced green fluorescent protein. Ideal for flow cytometry applications, fluorescence microscopy, and for experiments that require high accuracy.



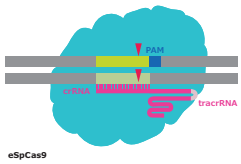
Wild-Type SpCas9

Original, wild-type Cas9; simple & economical; efficient in a broad range of gene editing applications



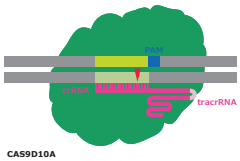
Enhanced Specificity eSpCas9

Cas9 variant with improved specificity ideal for experiments that require high accuracy.



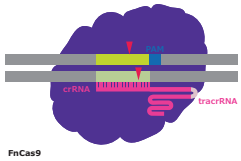
SpCas9 D10A Nickase

A 2-gRNA system with improved specificity and decreased off-target potential for specialized HDR genome editing applications.



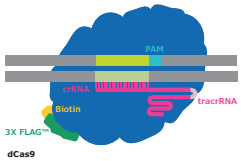
***Francisella novicida* Cas9**

Type II-B Cas9 protein that cleaves target DNA in a staggered pattern and can be used as a programmable restriction enzyme. Works for cloning and sequence enrichment in **cell-free environments**.



Dead SpCas9 3X Flag™

Catalytically inactive Cas9 protein ideal for DNA detection and isolation and is also a component of the proxy-CRISPR system.



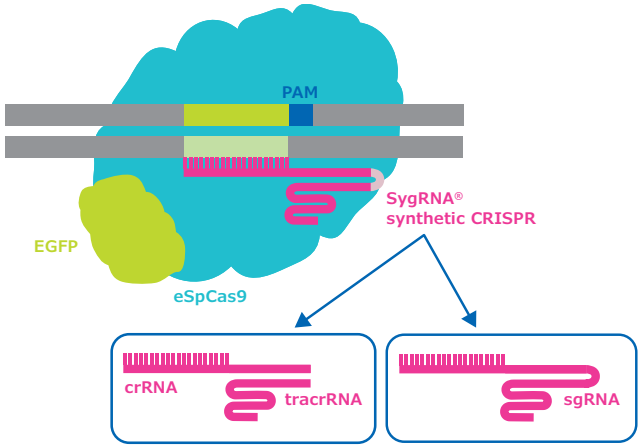


Figure 7. SygRNA® eSpCas9-GFP Ribonucleoprotein Complex

Table 5. Cas9 Protein Product Listings

Product Description	Cat. No.
Wild-Type Cas9 Protein	**CAS9PROT-50UG** **CAS9PROT-250UG** **CAS9PROT-2X250UG** **CAS9PROT-4X250UG**
Enhanced Specifity Cas9 Protein	**ESPCAS9PRO-50UG** **ESPCAS9PRO-250UG** **ESPCAS9PRO-2X250UG** **ESPCAS9PRO-4X250UG**
dCas9-3X FLAG™-Biotin Protein	**DCAS9PROT-50UG** **DCAS9PROT-250UG**
Francisella novicida Cas9 Protein	**FNCAS9PROT-50UG** **FNCAS9PROT-250UG**
Cas9-D10A Nickase Protein	**CAS9D10APR-50UG** **CAS9D10APR-250UG**
Cas9-GFP Protein	**CAS9GFPPRO-50UG** **CAS9GFPPRO-250UG** **CAS9GFPPRO-2X250UG** **CAS9GFPPRO-4X250UG**
Enhanced Specifity Cas9-GFP Protein	**ECAS9GFPPR-50UG** **ECAS9GFPPR-250UG** **ECAS9GFPPR-2X250UG** **ECAS9GFPPR-4X250UG**

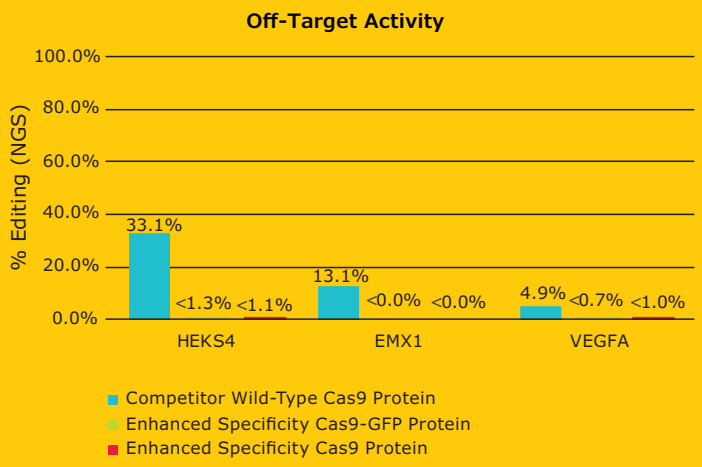
Cas9 protein storage – Reconstitute Cas9 protein with the provided reconstitution solution and store at –20 °C in a manual defrost freezer for up to one month. Aliquot and store at –70 °C long term.

*FnCas9 requires a unique tracrRNA, product number FNCAS9TRACR-5NMOL. For questions, visit **SigmaAldrich.com/AskAScientist**.

on target, on time

Enhanced Specificity eSpCas9 Plasmid and Protein

MISSION™ engineered eSpCas9 enhances on-target fidelity without loss of cleavage efficiency. Alanine point mutations were made in the chromosome-binding motif of SpCas9 (Slaymaker, et al, 2015) in an attempt to weaken non-specific Cas9 binding, increasing the pressure for precise match of gRNA to target. Tests of our eSpCas9 in combination with select gRNA demonstrated on-target cleavage efficiency comparable to wild-type SpCas9 with undetectable cleavage at select off-target sites.



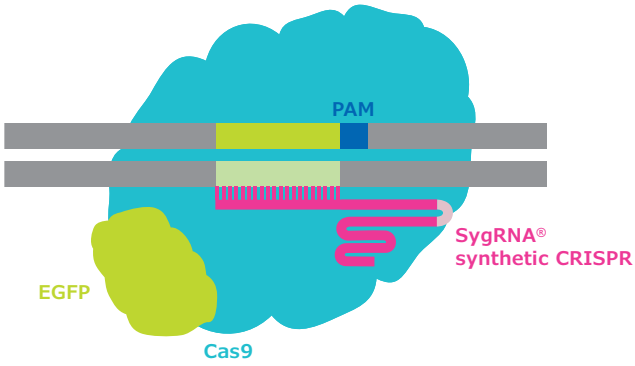
Enhanced specificity Cas9 (ESPCAS9PRO; red) and enhanced specificity Cas9-GFP (ECAS9GFPPR; green) have little or no detectable off target cutting compared to competitor wild-type Cas9 protein (cyan). 3 different genes targeted with a single synthetic sgRNA in HEK293T cells (n=3).

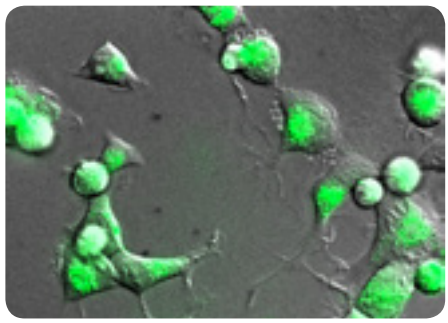
Find CRISPR proteins by visiting
SigmaAldrich.com/CRISPRproteins

MISSION™ Cas9-GFP and eSpCas9-GFP Fusion Proteins

Features and Benefits

- **Visible:** Cas9 fused to enhanced GFP for confirmation of delivery
- **Versatile:** Combine with one-part or two-part gRNAs delivered by transfection, electroporation or microinjection
- **Effective:** Engineered with three optimally configured nuclear localization signals for increased editing efficiency





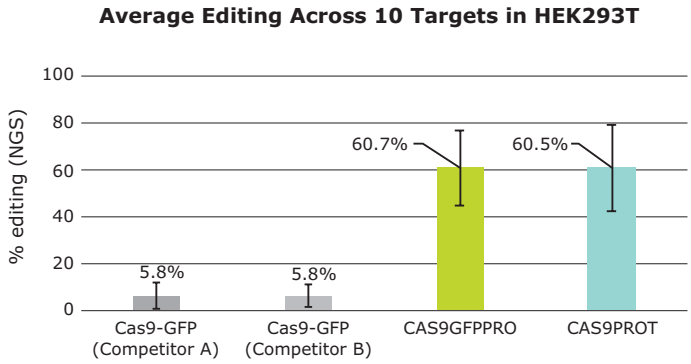


Figure 8.

CAS9GFPPRO edits at rates 10X higher than other commercially available Cas9-GFP fusion proteins with no loss in activity when compared to non-GFP fusion proteins.

Table 6. MISSION™ Cas9-GFP and eSpCas9-GFP Fusion Proteins

Product Name	Product Number
Wild-Type Cas9-GFP Protein	**CAS9GFPPRO-50UG** **CAS9GFPPRO-250UG** **CAS9GFPPRO-2X250UG** **CAS9GFPPRO-4X250UG**
Enhanced Specificity Cas9-GFP Protein	**ESPCAS9PRO-50UG** **ESPCAS9PRO-250UG** **ESPCAS9PRO-2X250UG** **ESPCAS9PRO-4X250UG**

For ordering and more, visit
SigmaAldrich.com/CRISPRproteins

CRISPR Goes Viral

The Leader in Lentiviral Manufacturing and Production

We lead the lentiviral manufacturing industry with over 10 years experience specializing in high-throughput, high titer, and large volume lentiviral production for projects large and small. Lentiviral CRISPR is ready-to-use and able to transduce virtually any mammalian cell line, including primary and non-dividing cells.

- Harness the power of CRISPR-Cas9 driven by lentiviral technologies
- Provide efficient delivery and stable expression of Cas9 and guide RNA
- Edit difficult to transfect cell types
- Permanently integrate Cas9, gRNA and selection markers
- Target virtually any sequence in any species
- Customize volume, titer and aliquots

LentiCRISPR Products

- Sanger QuickPick™ KnockOut gRNA
- Custom gRNA designs, panels, and pools
- LentiCRISPR gRNA-only, Cas9-only or All-In-One vector options
- Arrayed libraries
- Pooled libraries
- Controls (reference page 22)

For ordering and more, visit
SigmaAldrich.com/lentivirus

LentiCRISPR Vectors

Table 7. Lenti Vectors

Visit **SigmaAldrich.com/CRISPRessentials** for details about vector options.

Vector No.	Description	Cas9/gRNA Content	Selection Method
LV01	U6-gRNA:ef1a-puro-2A-Cas9-2A-tGFP	Cas9+gRNA	Fluorophore (GFP) & Puromycin
LV02	U6-gRNA:ef1a-puro	gRNA only	Puromycin
LV03	U6-gRNA:ef1a-tGFP	gRNA only	Fluorophore (GFP)
LV04	U6-gRNA:hPGK-puro-2A-tBFP	gRNA only	Fluorophore (BFP) & Puromycin
LV05	U6-gRNA:EF1a-Cas9+FLAG-2A-Puro	Cas9+gRNA	Puromycin
LV06	CRISPRa SAM U6-gRNA:ef1a-puro	gRNA only	Puromycin
LV07	CRISPRa SAM U6-gRNA:ef1a-zeo	gRNA only	Zeo

Available in bacteria glycerol stock, plasmid DNA and lentivirus formats

Table 8. Cas9 Lenti Product Listings

Cat. No.	LentiCRISPR Virus Format
CAS9BST-1EA	EF1a-Cas9-2A-Blasticidin Lenti Plasmid (Broad vector)
LVCAS9BST	EF1a-Cas9-2A-Blasticidin Lentiviral Particles (Broad vector)
CAS9NEO-1EA	EF1a-Cas9-2A-Neomycin Lenti Plasmid (Sigma-Aldrich vector)
LVCAS9NEO-1EA	EF1a-Cas9-2A-Neomycin Lentiviral Particles (Sigma-Aldrich vector)

Gene Panels Include:

- Apoptosis
- B Cell Activation
- Cancer Cell Biology
- Cell Adhesion
- Cell Cycle
- Cell Surface Proteins
- Cytokine & Cytokine Receptor
- DNA Repair
- Epigenetics
- GPCR
- Helicase
- Human Druggable
- Ion Channel
- JAK-STAT
- Kinase
- Membrane Trafficking
- Nuclear Hormone Receptors
- Phosphatase
- Proteases
- T Cell Activation
- Transcription Factors
- Tumor Suppressor
- Ubiquitin Enzymes
- Ubiquitin Proteases
- Ubiqutin Ligases

Sanger QuickPick™ KnockOut gRNA

We partnered with the Wellcome Sanger Institute to create a knockout gRNA collection with stringent design rules for targeted gene knockout in human and mouse genomes. Sanger QuickPick™ gRNA clones are available in glycerol, plasmid or lentiviral formats with convenient BFP reporter and puromycin selection cassettes.

Screen at Any Scale

The Sanger CRISPR library is the only tool that allows both whole genome knockout interrogation and sophisticated phenotypic readout in a convenient arrayed format. For smaller scale experiments, leverage the design expertise of the Wellcome Sanger Institute and our manufacturing quality to build a custom panel for your research.

Do you need more focused or affordable screens?

- Quick pick a single Sanger clone for any gene
- Cherry-pick a custom Sanger panel of any size
- Target any pathway or gene family with a Sanger panel
- Order any gRNA design in the Sanger vector

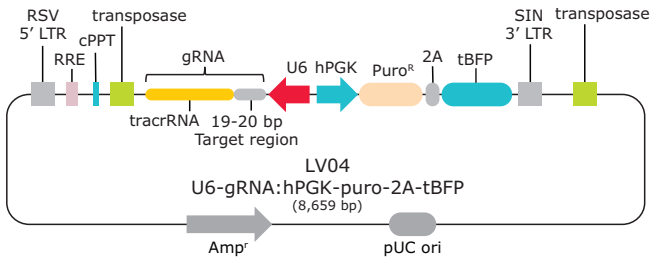


Table 9. Sanger QuickPick™ Knockout Clones

Cat. No.	Description
SANGERG	Human and Mouse Sanger QuickPick™ KO bacteria glycerol stock clones
SANGERD	Human and Mouse Sanger QuickPick™ KO plasmid DNA clones
SANGERV	Human and Mouse Sanger QuickPick™ KO lentivirus clones

Don’t see the option you need? Specify your own gRNA for manufacturing in the Sanger backbone. From whole genome libraries to individual clones, the Sanger CRISPR lentiviral collection is your path to unlimited discovery.

Visit **SigmaAldrich.com/AskaScientist** for more information.

Sanger Whole Genome Arrayed Lentiviral Libraries

The Next Generation of Screening Tools Has Arrived

In collaboration with the Wellcome Sanger Institute, the first-ever commercially available arrayed lentiviral CRISPR knockout libraries were created. Based upon validated techniques published in the literature, the Sanger CRISPR libraries will put your lab at the forefront of the race to make the next big discovery.

Content

- 2 knockout clones for every human and mouse protein-coding gene
- Nearly 40,000 sequence confirmed clones per species library

gRNA Design

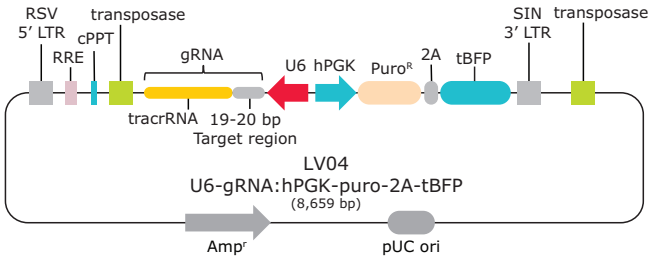
- Sanger clones maximize gene knockout by targeting the first half of the protein coding region while avoiding the first 90 bp
- Genomic target sequences are highly conserved, avoiding SNPs, to ensure representation in multiple cell lines
- Stringent design rules reduce or eliminate the potential for off-target effects

Vector

- Simplify the workflow with puromycin selection
- Illuminate CRISPR-expressing cells with BFP
- Flip the expression components in and out of the genome using transposase

Additional Features

- **Better, not bigger:** Two optimized clones per gene reduce the time, cost, and scale of screening experiments
- **Ready-to-screen:** Clones are arrayed in a robotics-friendly 96-well format for high throughput screening
- **Collaborative:** Real-time, library validation continues through the Wellcome Sanger Institute partnership



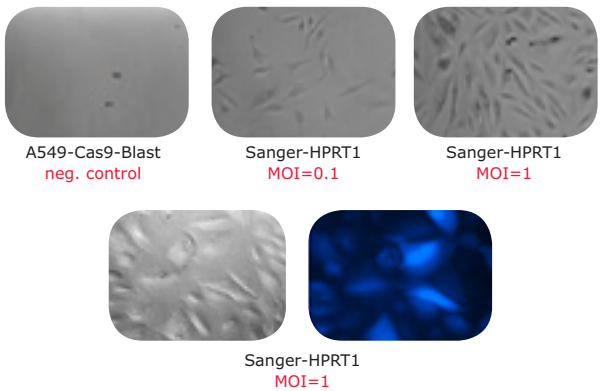


Figure 9.

Efficient viral transduction of A549 cells and CRISPR positive BFP illumination.

Table 10. Sanger Libraries

Cat. No.	Description
HSANGERG-1EA	Sanger Human Whole Genome Library, Glycerol stock
MSANGERG-1EA	Sanger Mouse Whole Genome Library, Glycerol stock
HSANGERV-1EA	Sanger Human Whole Genome Library, Lentiviral Particles
MSANGERV-1EA	Sanger Mouse Whole Genome Library, Lentiviral Particles

GeCKO and Sigma Lentiviral CRISPR Pooled Libraries

In partnership with Feng Zhang and the MIT/Broad Institute, we are proud to offer the improved GeCKOv2 libraries in high quality, ready-to-use lentiviral format. Individual CRISPR clones are also offered in the same GeCKOv2 vectors for follow-up validation of hits – another example of our dedication to bringing the power of CRISPR screening to every lab.

Table 11. Comparison chart of GeCKOv2 Pools versus Sigma Pools

GeCKOv2 Pooled Libraries	Sigma Pooled Library
Average of 6 gRNAs per gene, split between 2 pools	Average of 10 gRNAs per gene, all in the same pool
2 pools	8 pools (Human Genome); 1 pool (Human Kinase)
~62,000 gRNA clones per pool	~23,000 gRNA per Human Genome Pool; ~6,000 gRNA in Human Kinase Pool
Built in controls	Built in controls
Available in one vector system (GeCKO lentiCRISPRv2) OR 2 vector system (GeCKOv2 lentiGuide-Puro)	Human Library: 2 vector system (GeCKOv2 lentiGuide-Puro gRNA vector) Human Kinase Pool: All-in-one vector system (Sigma U6-gRNA:ef1a-puro-2A-Cas9-2A-tGFP)

Table 12. GeCKO and MISSION™ Lenti Particles

Cat. No.	Pooled LentiCRISPR Libraries	Vector No.
HGECKO2A-1EA	GeCKO2 Human Whole Genome CRISPR Pool, All-in-one Lenti Particles (GeCKO lentiCRISPRv2 vector)	LV05
HGECKO2G-1EA	GeCKO Human Whole Genome CRISPR Pool, gRNA Only Lenti Particles (GeCKOv2 lentiGuide-Puro vector)	LV02
HKCRISPR-1EA	Human Kinase Lentiviral CRISPR Pool	LV01
HWGCRISPR-1EA	Sigma Human Whole Genome CRISPR Pool, gRNA Only Lenti Particles (GeCKOv2 lentiGuide-Puro vector)	LV02
MGECKO2A-1EA	GeCKO2 Mouse Whole Genome CRISPR Pool, All-in-one Lenti Particles (GeCKO lentiCRISPRv2 vector)	LV05
MGECKO2G-1EA	GeCKO Mouse Whole Genome CRISPR Pool, gRNA Only Lenti Particles (GeCKOv2 lentiGuide-Puro vector)	LV02

Visit **SigmaAldrich.com/CRISPRessentials** for vector features and maps.

The GeCKOv2 lentiGuide-Puro and Sigma whole genome CRISPR pools are compatible with most Cas9 expressing cell lines. Our lenti-Cas9-Blast and lenti-Cas9-Neo vectors[1] are ideal for establishing stable Cas9 expression. Each pool in the GeCKO and Sigma Lentiviral CRISPR Pooled libraries is provided in 8 x 25 µL aliquots at a minimum titer of $5X10^8$ TU/mL (measured by p24 assay).

Features

- Single or Two-Vector Systems[2]
- 2-Vector System products are compatible with most Cas9 expressing cell lines for easy optimization
- Each pool provided in 8 x 25 µL aliquots at a minimum of $5x10^8$ viral particles/mL (via p24)

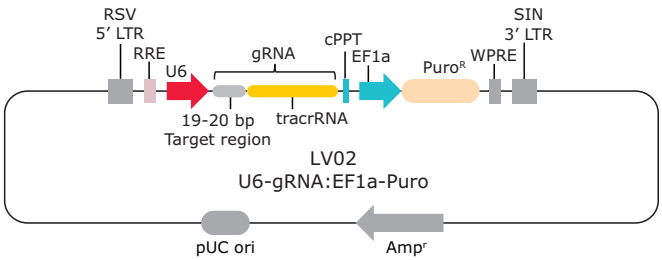
Benefits

- Screen the whole human and mouse genomes (>18,000 genes each) at the bench-top without robotics or specialized equipment
- Achieve gene knockout with 6 gRNAs per gene (GeCKO libraries) or 10 gRNAs per gene (Sigma library).
- Maximize CRISPR cleavage efficiency with consistent, puromycin-driven gRNA integration and expression
- Validate with confidence using built-in enrichment and depletion controls

[1]Product # CAS9BST, LVCAS9BST, CAS9NEO, LVCAS9NEO

[2]For screening applications where a single transduction experiment is desired, the all-in-one GeCKOv2 pooled libraries provide Cas9-gRNA-Puro on a single vector; Product # HGECKO2A, MGECKO2A

A) GeCKO v2 lentiGuide-Puro Vector



B) GeCKO lentiCRISPRv2 Vector

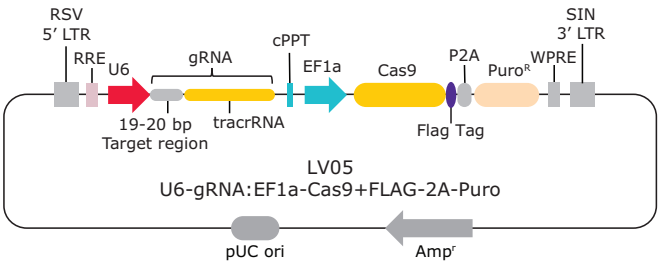


Figure 10.

GeCKOv2 CRISPR Vector Maps

CRISPR Kinase Pool: Results

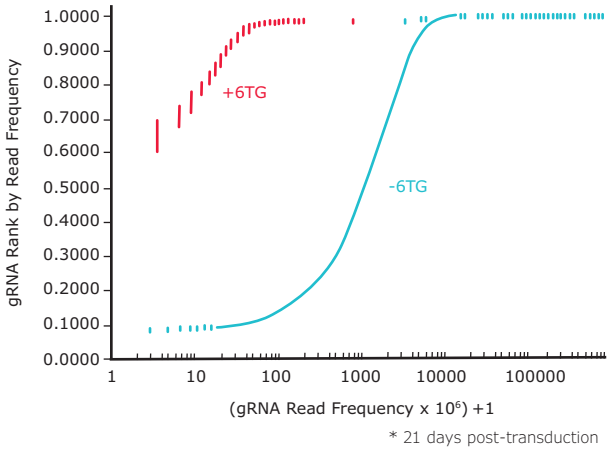


Figure 11.

Change in gRNA representation following 6-TG treatment of A549 cells

Deconvolution

Genomic DNA Prep and Deconvolution of CRISPR/Cas9, shRNA, and ORF Pools

Deconvolution services include a consultation pre- and post-screen for accurate experimental design and workflow setup to ensure optimal results.

Services to include:

- Genomic DNA extraction and/or DNA QC
- Target amplification with validated primer set
- Data provided in an easy-to-analyze format

Contact **MissionRNAi@sial.com** for quote information. Upon completion of your project, an electronic copy and USB drive with sequence data will be provided.

For more information, please visit SigmaAldrich.com/deconvolution.

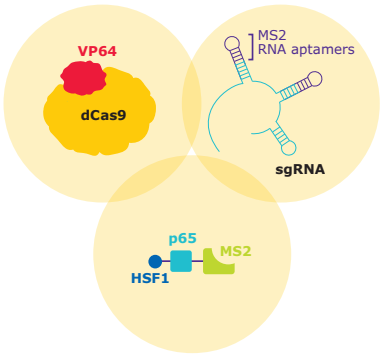
Estimated turn around time is 3 weeks.

Screening Deconvolution Workflow

Whole Genome CRISPRa Libraries

Synergistic Activation Mediator (SAM) lentivirus for gain-of-function screening

Assembled SAM Complex



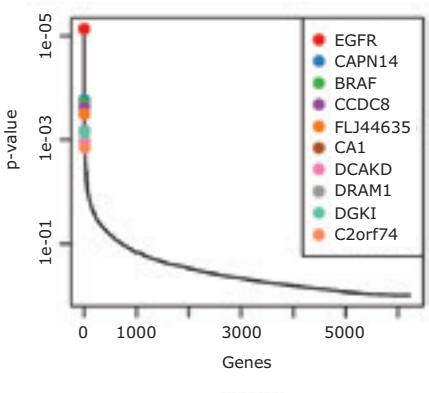


Figure 12. Enrichment Screen and Library Validation

A375 BRAF-mutant melanoma cells were screened for resistance to PLX4720-mediated cell death using the Pooled LentiCRISPR SAM Human Whole Genome Pooled Library Zeo Kit (pool 1 only). As reported in Konermann et al., 2015 *Nature*, guides targeting Epidermal Growth Factor Receptor (EGFR) for activation showed significant enrichment.

CRISPRa libraries supply human or mouse genome-wide transcriptional activation with enhanced delivery for long-term gene expression. SAM CRISPRa pools offer fast, easy, and cost-effective screening without the need for automation, liquid handling or robotics required for arrayed screens. Amplify your ability to uncover biological processes, pathways and functions through discovery of novel gene and drug targets involved in disease or development.

Ready-to-use Pooled Lentivirus

Each kit contains 8x25 µL aliquots of 5 different components:

- dCas9-VP64-Blasticidin
- MS2-P65-HSF1-Hygromycin
- 3 SAM CRISPRa Library Pools - choose Puro or Zeo

Library Construction

- gRNAs target 200 bp upstream of transcriptional start site to ensure activation
- Optimized lentiviral vectors have high functional titers for increased transduction efficiency
- Three gRNAs per gene equal more than 70,000 gRNAs targeting over 19000 genes
- Individual SAM library clones or custom gRNAs available for follow-up activation studies

Konermann S, et al. Genome-scale transcriptional activation by an engineered CRISPR-Cas9 complex. *Nature* 517 (2015): 583-588.

Find more at
SigmaAldrich.com/CRISPRa

Vector information can be found at
SigmaAldrich.com/CRISPRessentials

Table 13. Product Listings

Product	Cat. No.
SAM Helper Constructs: Plasmid DNA	
dCas9-VP64-Blasticidin SAM CRISPRa Helper Construct 1 Plasmid DNA	**SAMVP64BST-10UG**
MS2-P65-HSF1-Hygromycin SAM CRISPRa Helper Construct 2 Plasmid DNA	**SAMMS2HYG-10UG**
SAM CRISPRa Helper Construct Kit Plasmid DNA	**SAMHELPERP-1KT**
SAM Helper Constructs: Lentiviral Particles	
dCas9-VP64-Blasticidin SAM CRISPRa Helper Construct 1 Lentiviral Transduction Particles	**SAMVP64BSTV-8X25UL**
MS2-P65-HSF1-Hygromycin SAM CRISPRa Helper Construct 2 Lentiviral Transduction Particles	**SAMMS2HYGV-8X25UL**
SAM CRISPRa Helper Construct Kit Lentiviral Transduction Particles	**SAMHELPERV-1KT**
Whole Genome SAM CRISPRa Pooled Lentiviral Library Kits	
Human Whole Genome SAM CRISPRa Pooled Lentiviral Library Kit Zeo	**HSAMZEO-1KT**
Human Whole Genome SAM CRISPRa Pooled Lentiviral Library Kit Puro	**HSAMPURO-1KT**
Mouse Whole Genome SAM CRISPRa Pooled Lentiviral Library Kit Zeo	**MSAMZEO-1KT**
Mouse Whole Genome SAM CRISPRa Pooled Lentiviral Library Kit Puro	**MSAMPURO-1KT**

*Trans*IT-CRISPR® Transfection Reagent

Deliver various CRISPR reagent formats using *Trans*IT-CRISPR®, a novel polymeric transfection reagent that is convenient and simple to use.

- *Trans*IT-CRISPR® is a novel, non-liposomal polymeric transfection reagent for efficient delivery of CRISPR components
- Simple, fast, and versatile – deliver CRISPR DNA, RNA and RNP (Cas9-gRNA ribonucleoprotein complexes); also suitable for RNAi and ORF DNA and RNA formats
- Deliver CRISPR reagents to various cell types including difficult to transfect cells
- Exclusive distributor of *Trans*IT-CRISPR® made by Mirus Bio LLC

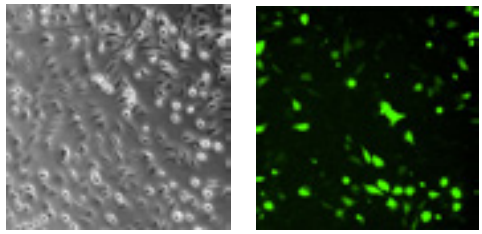


Figure 13.

High GFP expression using *Trans*IT-CRISPR® transfection reagent. Delivery of Cas9-GFP can easily be monitored by microscopy or FACS. U2OS cells were transfected with the MISSION™ CRISPR all-in-one vector containing gRNA targeting AAVS1.

For more information, visit
SigmaAldrich.com/transfectCRISPR

Table 14. Product Listings

Cat. No.	Description	Qty.
T1706-0.4ML **T1706-1ML**	*Trans*IT-CRISPR® Transfection Reagent	400 µL 1000 µL

Detection Products

Anti-CRISPR/Cas9 antibody, Mouse monoclonal clone 7A9-3A3, purified from hybridoma cell culture

Anti-CRISPR/Cas9 antibody, clone 7A9-3A3, raised against a recombinant protein fragment within the N-terminal region of Streptococcus pyogenes Cas9 (CRISPR/Cas9).

Features

- Mouse monoclonal antibody
- Purified from hybridoma cell culture
- Recognizes wild-type Cas9

Validated Applications

- Western Blot: 1-2 µg/mL
- Immunocytochemistry/Immunofluorescence: 1-2 µg/mL
- Immunoprecipitation: 5 µg per IP

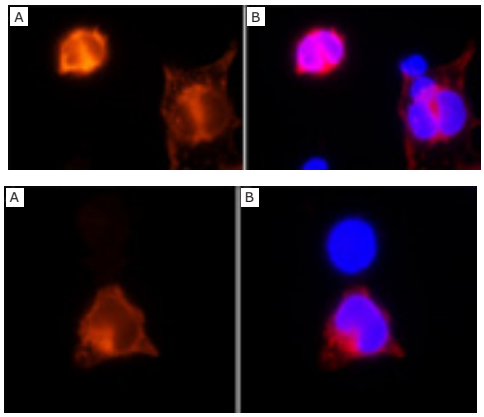


Figure 14.

Human HEK-293T cells overexpressing Cas9 were fixed and permeablized with 4% pararformaldehyde followed by 0.5% Triton X-100. Fixed cells were stained with 2 µg/mL Anti-CRISPR/Cas9, clone: 7A9-3A3 antibody (**Cat. No. SAV4200701**). The antibody was developed using Goat Anti-Mouse IgG, Cy3 conjugate (panel A). Cells were counterstained with DAPI (Blue) to stain nuclei (panel B).

Table 15. Product Listings

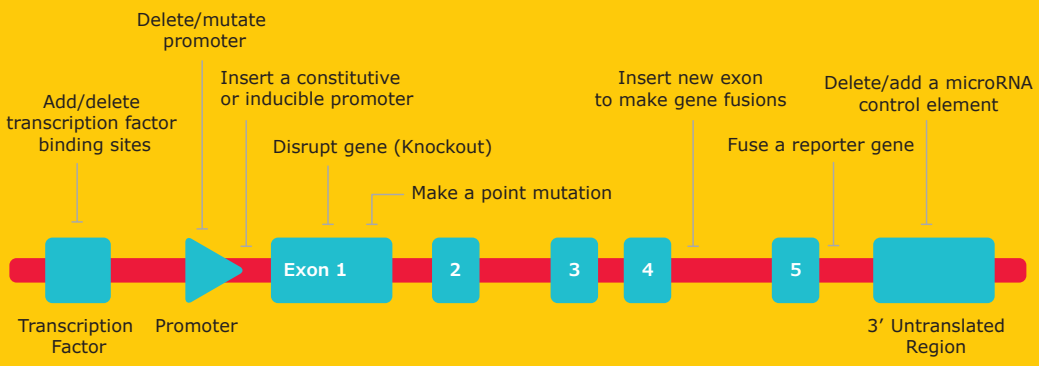
Cat. No.	Description	Clonality	Application
SAB4200701	Anti-CRISPR/Cas9 antibody, Mouse monoclonal, clone 7A9-3A3, purified from hybridoma cell culture	7A9-3A3, monoclonal	IP, IF
SAB4200735	Anti-CRISPR/CAS9 -FITC antibody, Mouse monoclonal, clone 7A9-3A3, purified from hybridoma cell culture	7A9-3A3, monoclonal	IF
SAB4200751	Anti-CRISPR/Cas9 (C-terminal) antibody, Mouse monoclonal, clone 10C11-A12, purified from hybridoma cell culture	10C11-A12, monoclonal	IP, IF

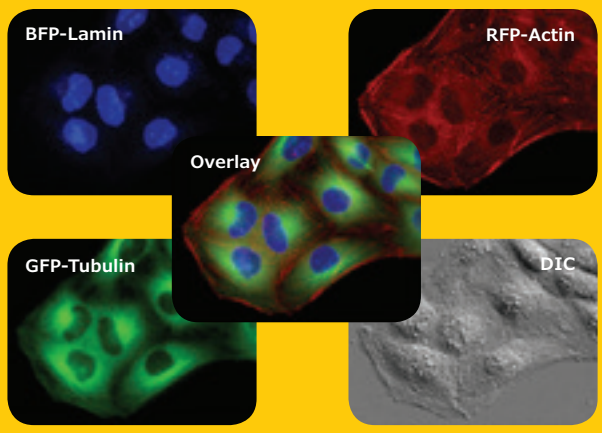
cell design studio™ services

Cellular Models Tailored to Your Needs

With best-in-class capabilities and expertise in genome editing, the Cell Design Studio™ team are the research partner you can trust to deliver customized cellular models for your drug discovery and disease modeling research.

Genome Editing Possibilities with Cell Design Studio™ Services





Triple-tagged reporter cell line used for high content imaging and small molecule screening

Customized Immunotherapy Research Models

- Potency & Specificity Assays
- Tumor Antigen Expression
- T-Cell Receptor Modifications
- Checkpoint Inhibitor Expression
- Producer Cell Line Enhancement

Endless Drug Discovery and Cell-Based Assay Applications

The Cell Design Studio™ team helps researchers create more predictive research models for their drug discovery applications.

- Disease Modeling
- Cellular Reporters
- Drug Screening
- Target ID/Validation

The CDS Advantage

- **More deliverables** – Delivery of up to three (3) clones and wild-type controls of your engineered cell line
- **Ownership of IP rights** - CDS customers own their custom engineered cell lines
- **Milestone-based pricing and project management** - Minimize project risk and maximize flexibility
- **Unmatched expertise** – CDS has engineered over 300 different genes in over 200 parental cell lines
- **Collaborative Design** - Direct consultation with R&D scientists yields better models
- **Recent technology and automation investments** - shortened timelines and increase project success rate

CRISPR Workflow

Your screen begins with the right reagents

Visit us at **SigmaAldrich.com** to choose from the full spectrum of products needed to perform your experiment. From cell lines to oligos, and everything in between, we have you covered.

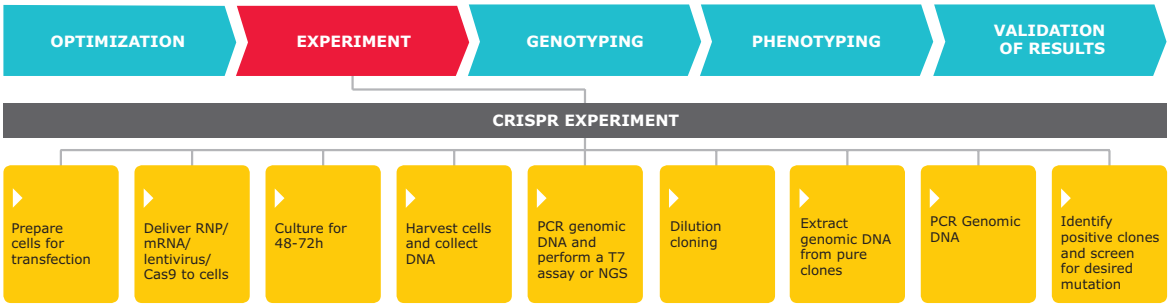


Table 16. Popular Associated CRISPR Experiment Reagents

Cat. No.	Associated CRISPR Experiment Reagents
D6171	Dulbecco's Modified Eagle's Medium - high glucose, HEPES modification
D8537	Dulbecco's Phosphate Buffered Saline
D5796	Dulbecco's Modified Eagle's Medium - high glucose
P4333	Penicillin-Streptomycin
T3924	Trypsin-EDTA solution
G7513	L-Glutamine solution
CLS430720	Corning® cell culture flasks, 75 cm^2
CLS430825	Corning® cell culture flasks, 150 cm^2
CLS431082	Corning® cell culture flask, 225 cm^2
CLS430290	Corning® 50 mL centrifuge tubes
G5516	Glycerol
T5574	Terrific Broth
G3169	GC5™ Competent Cells
P9620	Puromycin Dihydrochloride Ready Made Solution
T1706	*Trans*IT-CRISPR® Transfection Reagent
NA0410	GenElute™ HP Endotoxin-Free Plasmid Maxiprep Kit
NA9604	GenElute™ HP 96-Well Plasmid Miniprep Kit
NA1020	GenElute™ PCR Clean-Up Kit
RTN350	GenElute™ Mammalian Total RNA Miniprep Kit
T9424	TRI Reagent® RNA Isolation Reagent
D3687	DirectLoad™ PCR 100 bp Low Ladder
D7058	DirectLoad™ Wide Range DNA Marker

Cat. No.	Associated CRISPR Experiment Reagents
D9307	JumpStart™ Taq DNA Polymerase
P0982	JumpStart™ REDTaq® ReadyMix™ Reaction Mix
R2523	REDTaq® ReadyMix™ PCR Reaction Mix
D1806	Taq DNA Polymerase from *Thermus aquaticus*
CLS4487	Corning® Costar® Stripette® serological pipettes, 5 mL
CLS4489	Corning® Costar® Stripette® serological pipettes, 25 mL
CLS4490	Corning® Costar® Stripette® serological pipettes, 50 mL
HT90132	Crystal violet solution
15205	Blasticidine S hydrochloride
H0654	Hygromycin B solution from *Streptomyces hygroscopicus*
G1N70	GenElute™ Mammalian Genomic DNA Miniprep Kits
C2874	CryoStor® cell cryopreservation media
H6648	Hanks' Balanced Salt solution
H9268	Hexadimethrine bromide
D8662	Dulbecco's Phosphate Buffered Saline With $MgCl_2$ and $CaCl_2$
HSOLIGOINT	CRISPR Integration Kit - Use to determine baseline for Homology Directed Repair for cell lines
SHP002	CRISPR & MISSION® Lentiviral Packaging Mix
XTG360-RO	X-tremeGene™ 360 Transfection Reagent

CRISPR Controls

Cat. No.	Description	Vector	Control Type	System	Format	gRNA Type	Selection Method
CRISPR06	CRISPR Universal Non-target Negative Control 1, Cas9+gRNA Plasmid	p01	Neg.	Mammalian	Plasmid DNA	Cas9+gRNA	Fluorophore (GFP)
CRISPR07	CRISPR Universal Non-target Negative Control 2, Cas9+gRNA Plasmid	p01	Neg.	Mammalian	Plasmid DNA	Cas9+gRNA	Fluorophore (GFP)
CRISPR08	CRISPR Universal Non-target Negative Control 3, Cas9+gRNA Plasmid	p01	Neg.	Mammalian	Plasmid DNA	Cas9+gRNA	Fluorophore (GFP)
CRISPR17	CRISPR Activator Human Oct4 Positive Control Plasmid, gRNA Only Expression Plasmid	p03	Pos.	Mammalian	Plasmid DNA	gRNA only	
CRISPR12	CRISPR-Lenti Universal Non-Target Negative Control 1, Cas9+gRNA Lenti Plasmid (Sigma vector)	LV01	Neg.	Lentiviral	Plasmid DNA	Cas9+gRNA	Fluorophore (GFP) & Puromycin
CRISPR18	CRISPR-Lenti Universal Non-target Negative Control 1, gRNA Only Lenti Plasmid (Sanger vector)	LV04	Neg.	Lentiviral	Plasmid DNA	gRNA only	Fluorophore (BFP) & Puromycin
CRISPR19	CRISPR-Lenti Universal Non-target Negative Control 2, gRNA Only Lenti Plasmid (Sanger vector)	LV04	Neg.	Lentiviral	Plasmid DNA	gRNA only	Fluorophore (BFP) & Puromycin
CRISPR20	CRISPR-Lenti Universal Non-target Negative Control 3, gRNA Only Lenti Plasmid (Sanger vector)	LV04	Neg.	Lentiviral	Plasmid DNA	gRNA only	Fluorophore (BFP) & Puromycin
CRISPR12V	CRISPR-Lenti Universal Non-Target Negative Control 1, Cas9+gRNA Lentiviral Particles (Sigma vector)	LV01	Neg.	Lentiviral	Lentivirus	Cas9+gRNA	Fluorophore (GFP) & Puromycin

Cat. No.	Description	Vector	Control Type	System	Format	gRNA Type	Selection Method
CRISPR12H	CRISPR-Lenti Universal Non-Target Negative Control 1, Cas9+gRNA Lentiviral Particles, High Titer (Sigma vector)	LV01	Neg.	Lentiviral	Lentivirus	Cas9+gRNA	Fluorophore (GFP) & Puromycin
CRISPR15H	Gecko2-Lenti Universal Non-Target Negative Control 1, gRNA Only High Titer Lentiviral Particles (Gecko2 vector)	LV02	Neg.	Lentiviral	Lentivirus	gRNA only	Puromycin
CRISPR18V	CRISPR-Lenti Universal Non-target Negative Control 1, gRNA Only Lentiviral Particles (Sanger vector)	LV04	Neg.	Lentiviral	Lentivirus	gRNA only	Fluorophore (BFP) & Puromycin
CRISPR19V	CRISPR-Lenti Universal Non-target Negative Control 2, gRNA Only Lentiviral Particles (Sanger vector)	LV04	Neg.	Lentiviral	Lentivirus	gRNA only	Fluorophore (BFP) & Puromycin
CRISPR20V	CRISPR-Lenti Universal Non-target Negative Control 3, gRNA Only Lentiviral Particles (Sanger vector)	LV04	Neg.	Lentiviral	Lentivirus	gRNA only	Fluorophore (BFP) & Puromycin
CRISPR01	CRISPR Human EMX1 Positive Control Plasmid, gRNA Only Expression Plasmid, includes Cas9 Expression Plasmid (Sigma vector)	p03	Pos.	Mammalian	Plasmid DNA	gRNA only	
CRISPR02	CRISPR Nickase Human EMX1 Positive Control Plasmids (gRNA Only Expression Plasmids, Includes Cas9-D10A Plasmid)	p03	Pos.	Mammalian	Plasmid DNA	gRNA only	
CRISPR11	CRISPR-Lenti Human EMX1 Positive Control, Cas9+gRNA Lenti Plasmid (Sigma vector)	LV01	Pos.	Lentiviral	Plasmid DNA	Cas9+gRNA	Fluorophore (GFP) & Puromycin
CRISPR13	CRISPR-Lenti Human HPRT1 Positive Control, Cas9+gRNA Lenti Plasmid (Sigma vector)	LV01	Pos.	Lentiviral	Plasmid DNA	Cas9+gRNA	Fluorophore (GFP) & Puromycin
CRISPR21	CRISPR-Lenti Human HPRT1 Positive Control, gRNA Only Lenti Plasmid (Sanger vector)	LV04	Pos.	Lentiviral	Plasmid DNA	gRNA-only	Fluorophore (BFP) & Puromycin

Cat. No.	Description	Vector	Control Type	System	Format	gRNA Type	Selection Method
CRISPR11V	CRISPR-Lenti Human EMX1 Positive Control, Cas9+gRNA Lentiviral Particles (Sigma vector)	LV01	Pos.	Lentiviral	Lentivirus	Cas9+gRNA	Fluorophore (GFP) & Puromycin
CRISPR13V	CRISPR-Lenti Human HPRT1 Positive Control, Cas9+gRNA Lentiviral Particles (Sigma vector)	LV01	Pos.	Lentiviral	Lentivirus	Cas9+gRNA	Fluorophore (GFP) & Puromycin
CRISPR13H	CRISPR-Lenti Human HPRT1 Positive Control, Cas9+gRNA Lentiviral Particles, High Titer (Sigma vector)	LV01	Pos.	Lentiviral	Lentivirus	Cas9+gRNA	Fluorophore (GFP) & Puromycin
CRISPR16H	Gecko2-Lenti Human HPRT1 Positive Control, gRNA Only High Titer Lentiviral Particles (Gecko2 vector)	LV02	Pos.	Lentiviral	Lentivirus	gRNA only	Puromycin
CRISPR21V	CRISPR-Lenti Human HPRT1 Positive Control, gRNA Only Lentiviral Particles (Sanger vector)	LV04	Pos.	Lentiviral	Lentivirus	gRNA only	Fluorophore (BFP) + Puromycin
CRISPRPL01	CRISPR GUS GAPDH Reporter Control for Monocots	p62	Pos.	Plant	Plasmid DNA	Cas9+gRNA	Beta Glucuronidase
CRISPRPL02	CRISPR GUS GAPDH Reporter Control for Dicots	p63	Pos.	Plant	Plasmid DNA	Cas9+gRNA	Beta Glucuronidase

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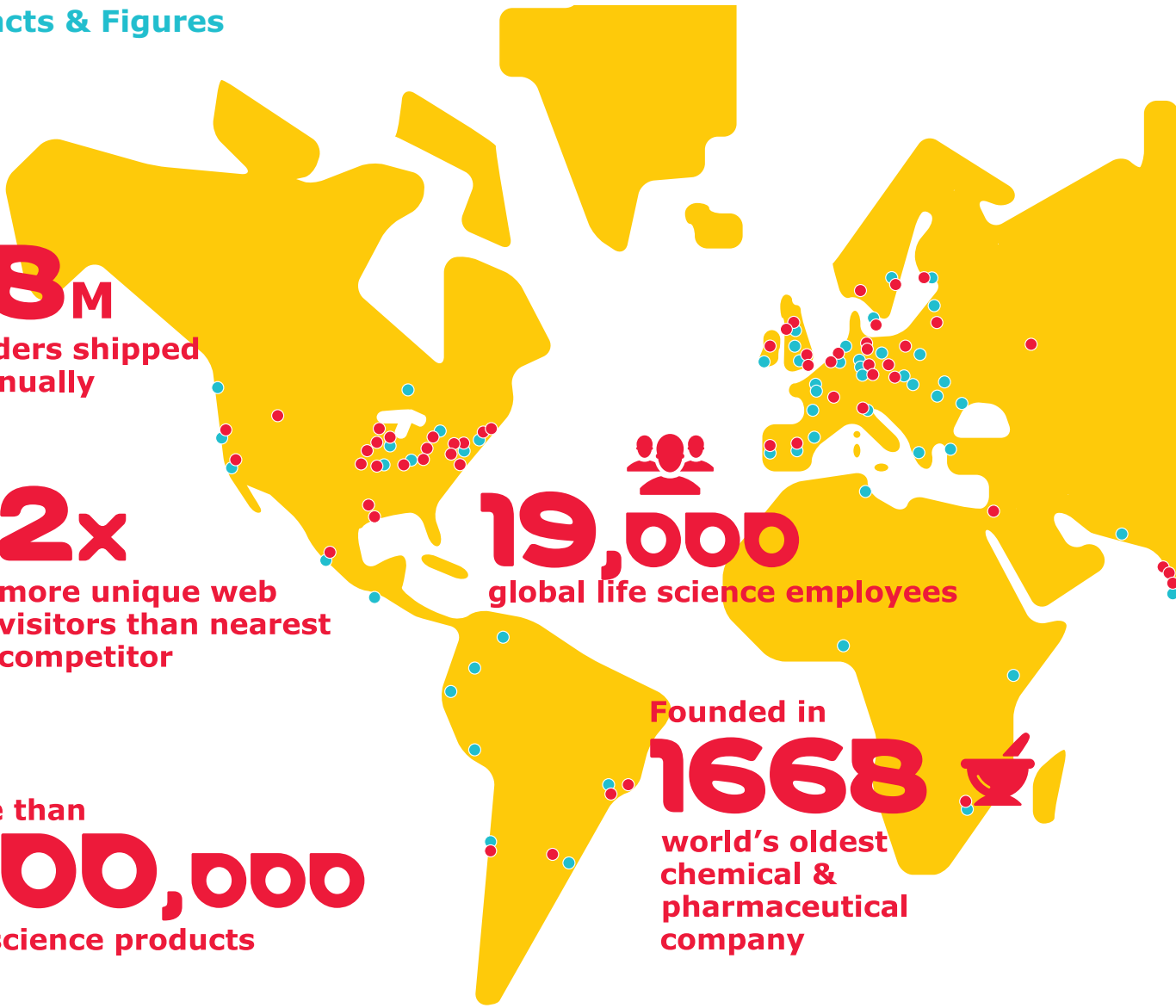

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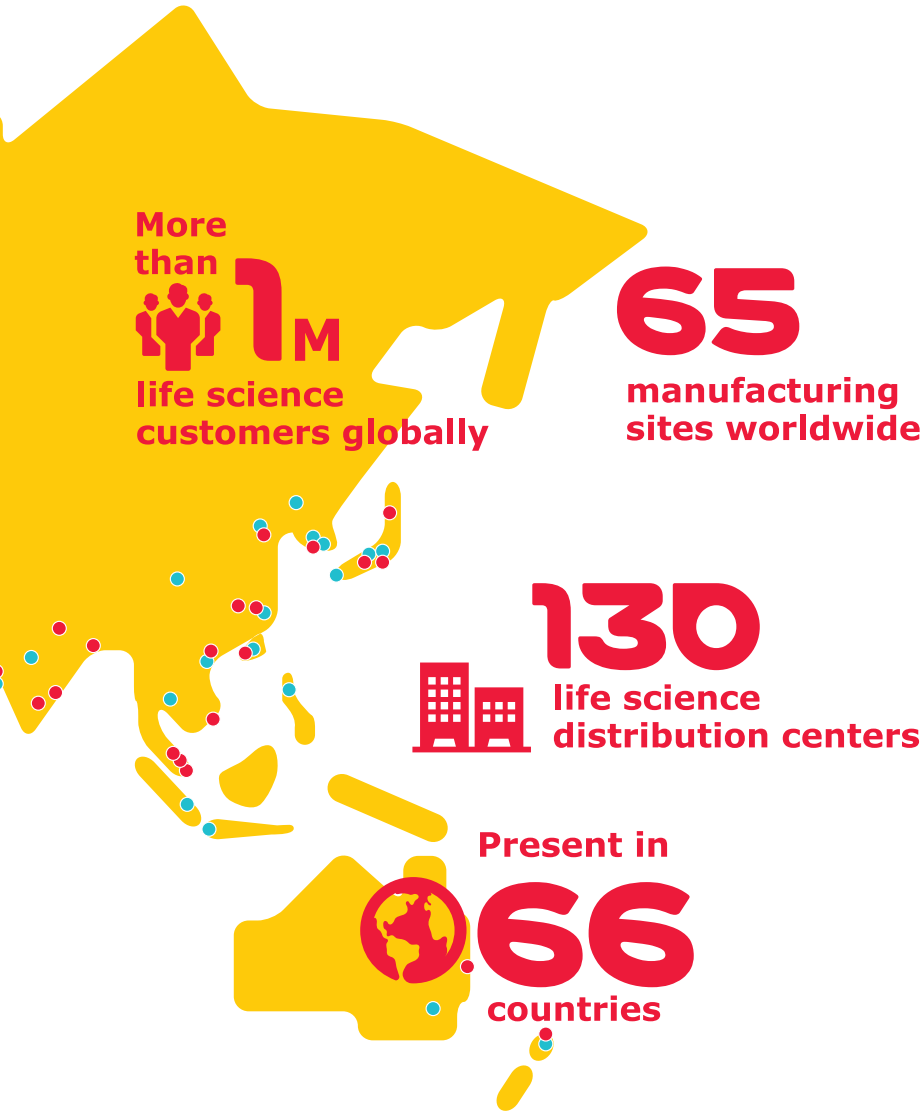

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