

Knock Down Your Favorite Genes with Ease and Confidence



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Questions? Comments? or Suggestions?

Ask now or contact Technical Support

M – F, 9 AM – 6 PM EST.

Telephone: 888-503-3187; Email: support@SABiosciences.com

■ Introduction

- RNA Interference: Why use RNAi?
- How does siRNA and shRNA work?
- Challenges
- Solutions

■ siRNA

- Types of siRNA available from QIAGEN
- Protocol/Optimizations
- Research Applications (transient screening, high throughput)

■ shRNA

- shRNA plasmids: maps, features and utility
- Optimizations
- Research Applications (permanent knockdown or transient selection)

■ Validation of RNAi Experiments

■ Summary

- Pilot Study Offer for shRNA and Gene Expression

■ Why knock down the expression of a gene?

- Gene function studies
- Remove protein activity
- Signaling pathway studies

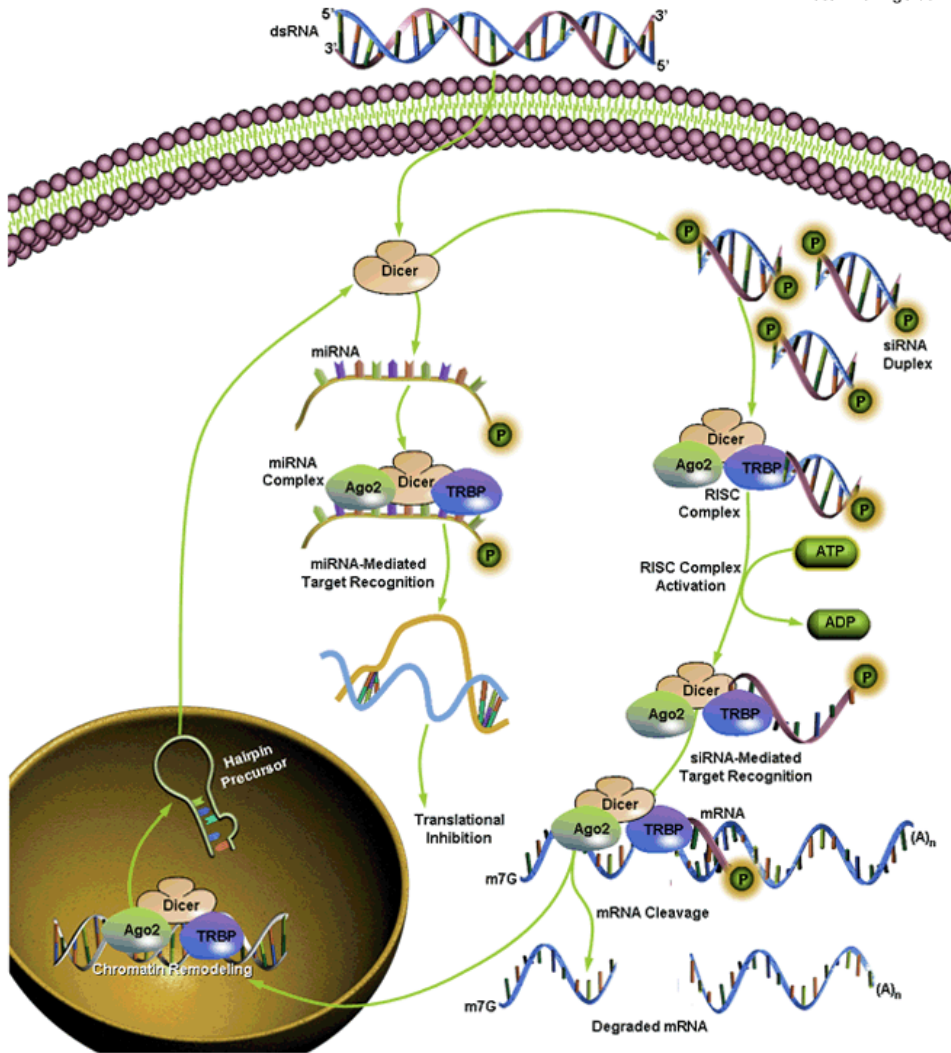
■ Methods of RNAi

- siRNA – short interfering RNA, chemical or enzymatically synthesized
 - siRNA directly delivered through transfection/electroporation
- shRNA – short hairpin RNA, plasmid or viral based expression vector
 - Vector is delivered to the cell which then produces shRNA

RNA Interference – How It Works

SABiosciences™

www.SABiosciences.com
www.ProteinLounge.com



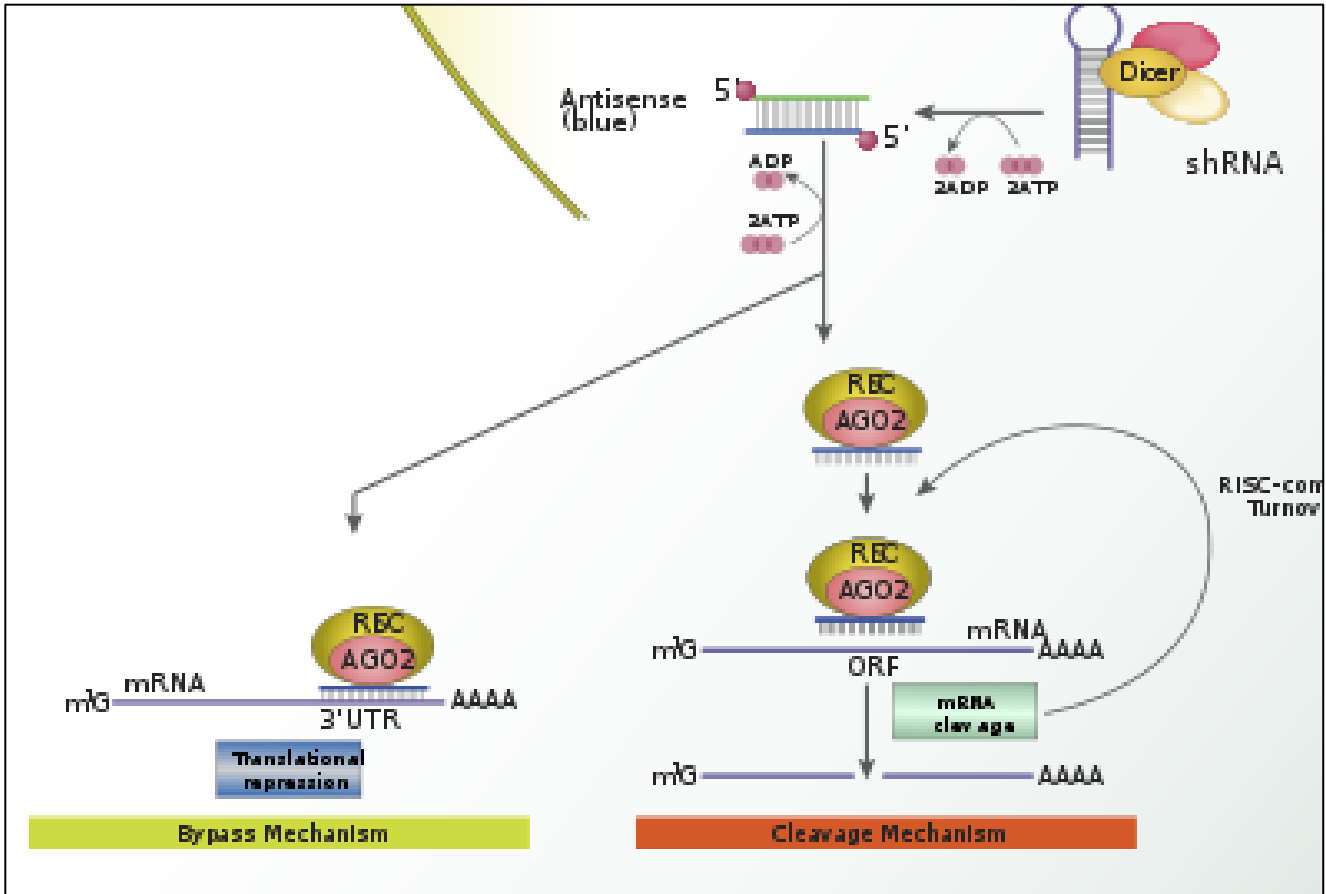
• What is siRNA?

- siRNAs are 21–23nt (nucleotide) dsRNA duplexes with symmetric 2–3nt 3' overhangs and 5'-phosphate and 3'-hydroxyl groups

• How it works

- Dicer delivers the siRNAs to a group of proteins called the RISC (RNA-Inducing Silencing Complex)
- siRNA duplex unwinds
- Once unwound, the single-stranded antisense strand guides RISC to mRNA that has a complementary sequence

shRNA- How it Works



- **What are shRNA**
 - Small hairpin RNA
- **How it works**
 - A vector is introduced into cells and utilizes the U1 promoter to ensure that the shRNA is always expressed.
 - Dicer cleaves the shRNA into siRNA.
 - The siRNA gene silencing mechanism is followed.

■ RNAi Knock Down Effectiveness

- Differences exist between:
 - Knockdown efficiencies advertised by companies, reported in the literature
 - Knockdown efficiencies observed by researchers

■ RNAi Specificity

- Insure phenotype only due to the knockdown of target gene(s)
 - Minimize “off-target” effect
 - Minimize toxic side-effects of delivery and RNAi
 - Watch out for Immune/ Physiological Responses to RNAi

SABiosciences SureSilencing shRNA

- **Multiple Designs for Optimization: 2 out of 4 guarantee to suppress gene expression by 70%**
 - 4 plasmids with different designs for shRNA
 - Algorithm
 - Smith-Waterman (optimal) vs BLAST (efficient) sequence alignment
 - Length, GC content, thermostability
 - Experimentally Tested and Refined Algorithm
- **Ease of use & compatible with cell and gene-targeting assays**
 - Negative control included
 - Unlimited supply/sequence information provided
 - Ability to select permanent cell line/ Enrich for transfected cells



Solution: Multiple Designs and Delivery of Validated RNAi and Experimental Controls

QIAGEN Flexitube/Flexitube pre-mix/Flexiplate siRNA

- **FlexiTube siRNA**
 - Predesigned human, mouse and rat siRNA

- **FlexiTube siRNA Premix**
 - Optimized mix of human or mouse siRNA + transfection reagent

- **FlexiPlate siRNA**
 - Flexible siRNA sets for customer-specified genes and siRNA controls
 - (96 or 384 well format for HTP screening applications)

- **AllStars RNAi Controls**
 - Molecularly characterized controls for Human, Mouse and Rat siRNA experiments



Flexitube siRNAs: Thousands of tested and validated designs

Cutting Edge Design: HP On-Guard Algorithm was experimentally validated using wet-bench results

Thousands of Experimentally Validated Designs: Ready to be ordered to cut down on optimization

Full siRNA sequence: Can be used to for publishing results.



Features of HP On-Guard Design Algorithm

Asymmetry: siRNAs are designed with unequal stabilities of the base pairs at the 5' ends. This enables the antisense strand, which is less tightly bound at its 5' end, to enter RISC, while the sense strand is degraded. Asymmetry produces highly functional siRNAs and reduces the risk of off-target effects caused by the incorrect strand entering RISC.

3' UTR/seed region analysis: Intelligently weighted, multi-parameter searches for matches of the seed region of the siRNA antisense strand with the 3' untranslated region of unintended mRNA targets are performed. See detailed explanation below.

SNP avoidance: The RefSNP database is used to exclude siRNAs which span single nucleotide polymorphisms (SNPs). This increases siRNA potency, as an siRNA spanning a SNP will vary in its effectiveness.

Interferon motif avoidance: siRNAs are screened for multiple sequence motifs known to result in an interferon response. siRNAs with such motifs are rejected.

Neural-network technology: siRNA design uses the BioPredsi neural-network which is based on an extremely large RNAi data set

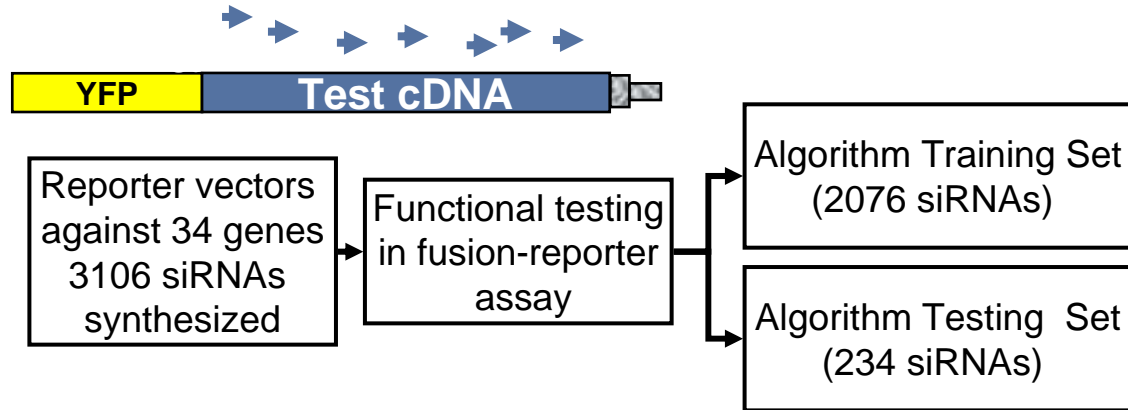
The world's largest siRNA validation project: Data from this project, in which QIAGEN scientists proved the effectiveness of thousands of siRNAs, were used to reinforce and improve the design process. A large number of druggable genome siRNAs have been proven to provide at least 70% knockdown during this project.

Homology analysis: A proprietary tool and an up-to-date, nonredundant sequence database are used.

Affymetrix GeneChip analysis: Genomewide analysis enabled development of siRNA design improvements that minimize off-target effects.

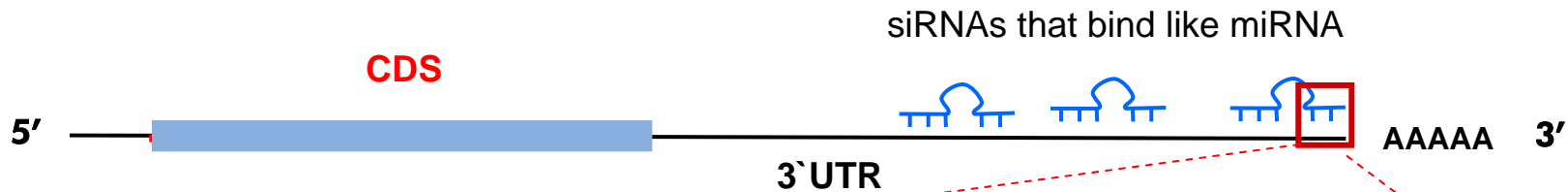
Up-to-date siRNA target sequences: Current data from NCBI databases ensure accurate design.

BioPredsi algorithm:



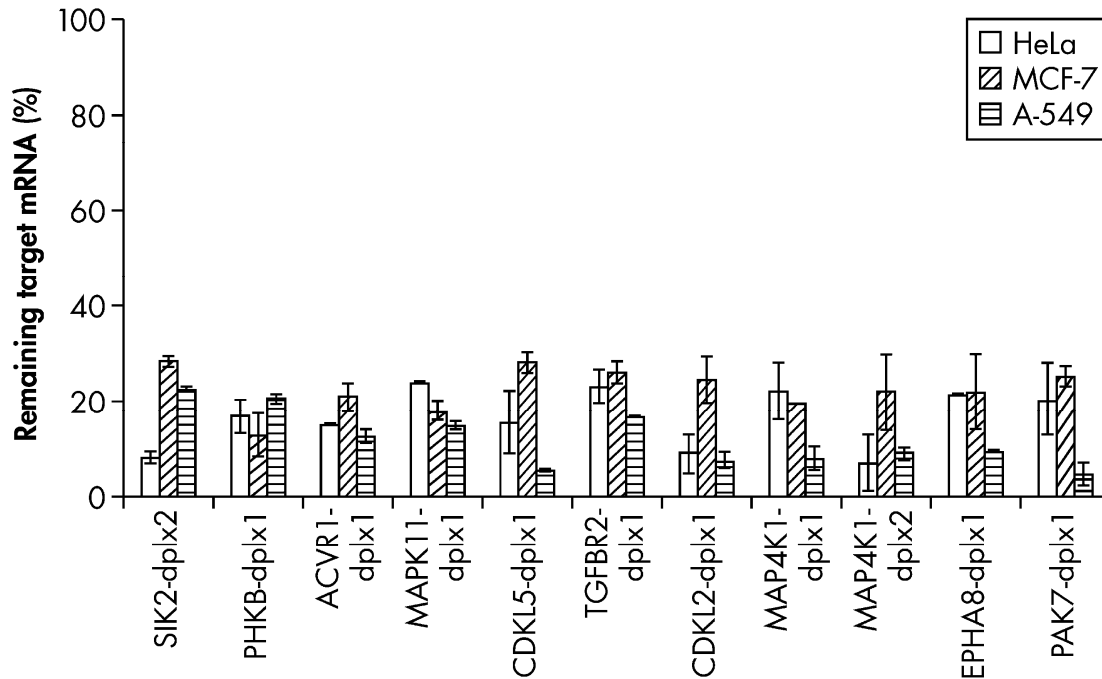
(Hall. et al. Nature Biotechnology July 2005)

3' UTR-Seed Region Analysis



■ Seed region

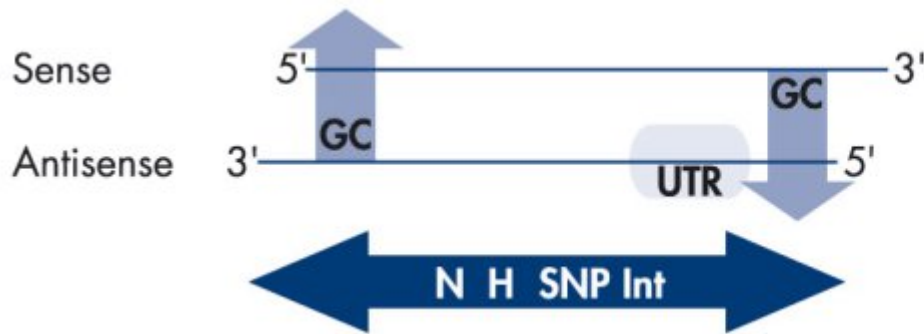
- Position 2-7 of miRNA / siRNA sequence
- miRNA binding to mRNA through seed region
- Presence of multiple seed region matches increases likelihood of off-target effects



- Experimentally proven functionality
- Per siRNA 8 independent data points (replications etc.)
- Largest validated siRNA set (> 3700 siRNAs)
- Algorithm feeds validation, validation feeds algorithm
- QIAGEN algorithm based on ~ 8000 siRNAs (3000 genes)

Krüger et al., 2007; Insights into Effective RNAi Gained from Large-Scale siRNA Validation Screening. *Oligonucleotides* 17:237–250

Summary of HP-On Guard Design Algorithm



GC	GC asymmetry
UTR	UTR/seed region analysis
N	Neural-network technology
H	Homology analysis
SNP	SNP avoidance
Int	Interferon motif avoidance

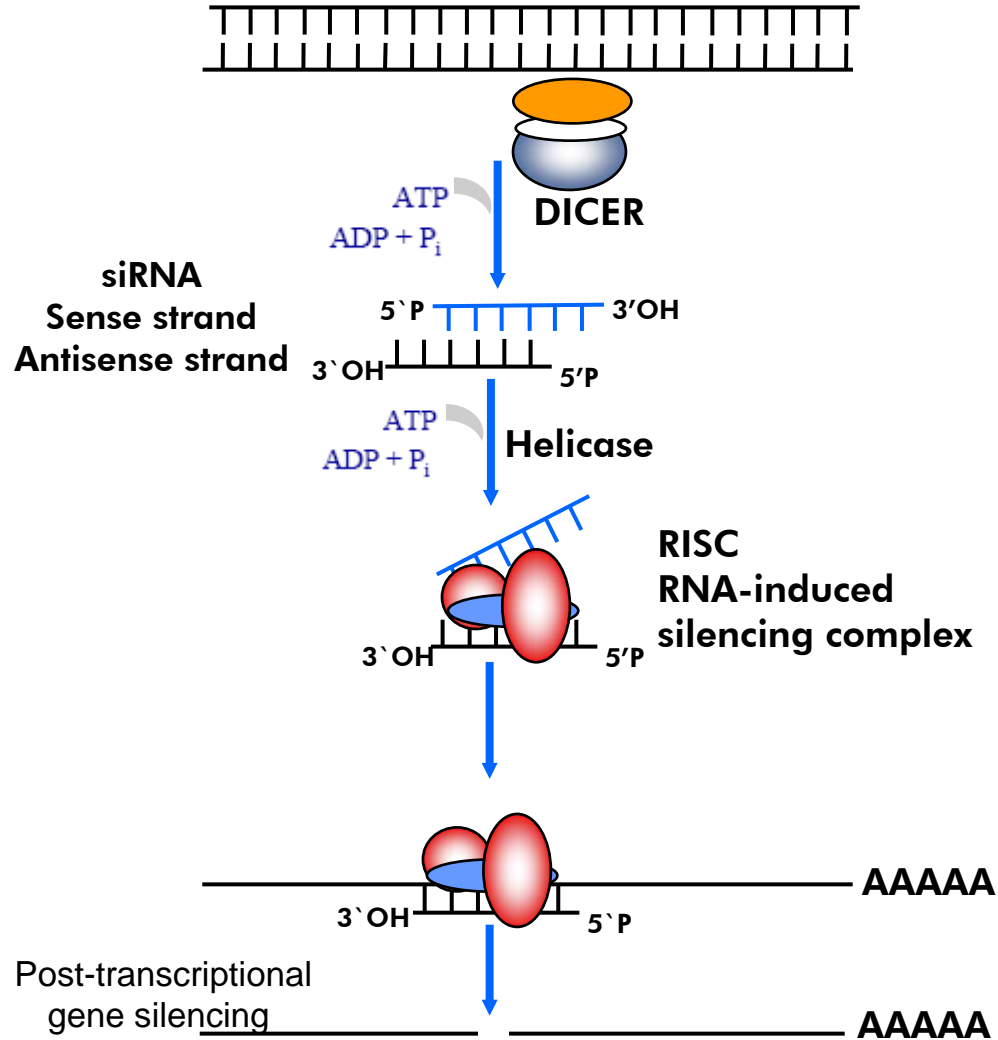
Sequence-specific off-target effects

- siRNA targeting mRNA with close homology
- siRNAs functioning like miRNAs

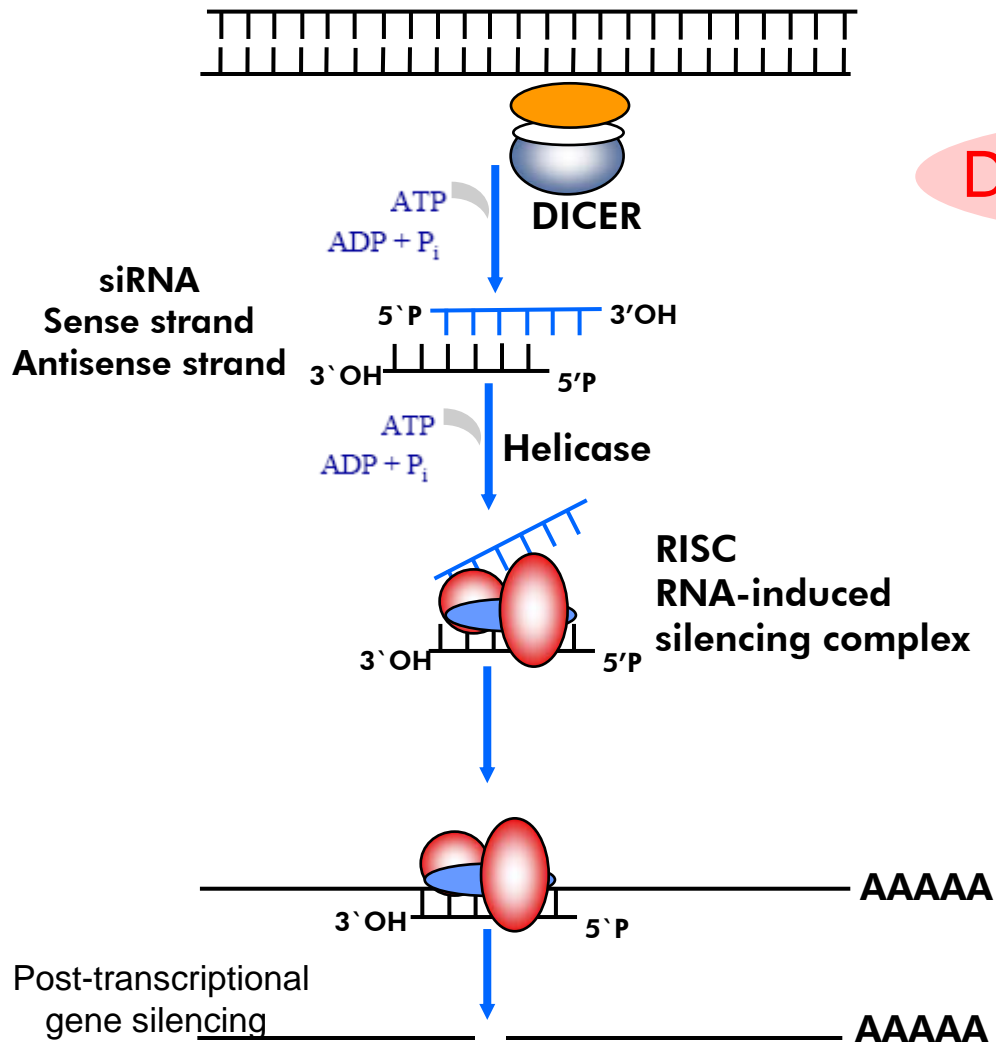
Non-sequence-specific off-target effects

- Cellular response to RNAi toxicity

Off-Target Effects



Off-Target Effects

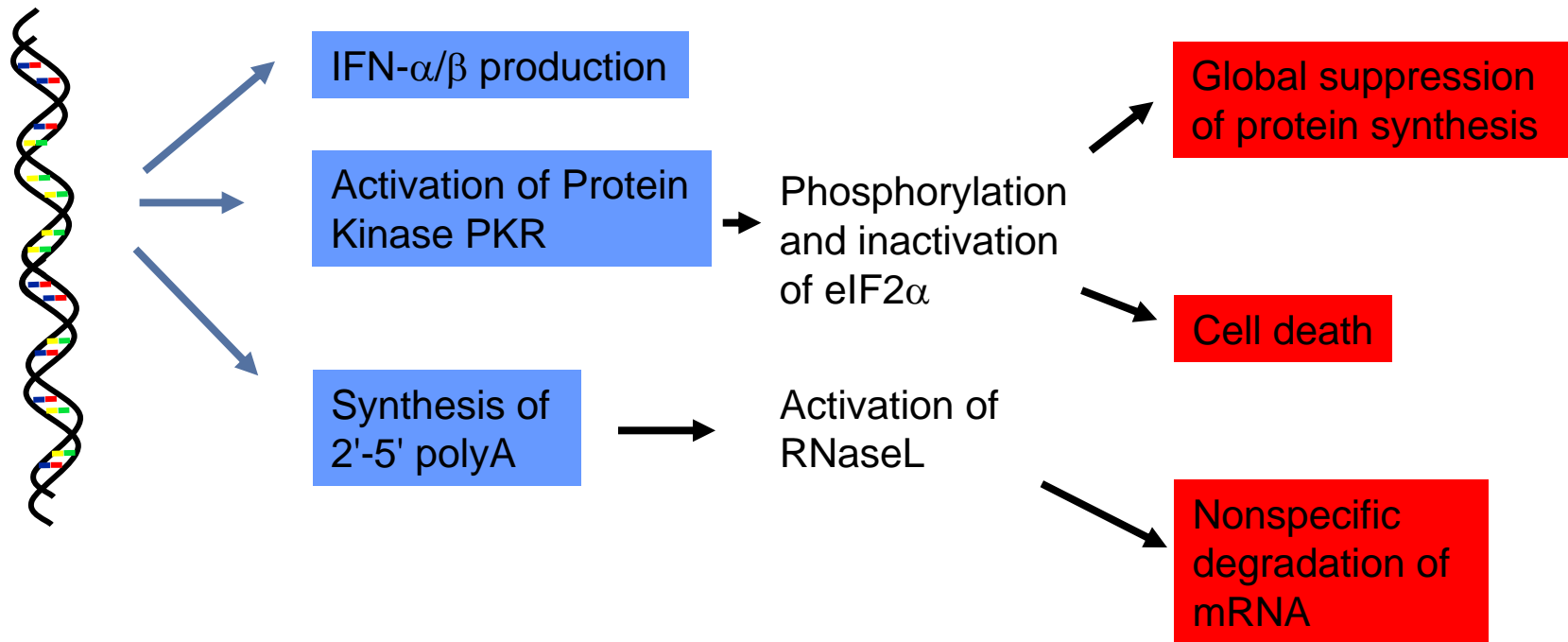


Defense mechanism

miRNA effects

Target specificity

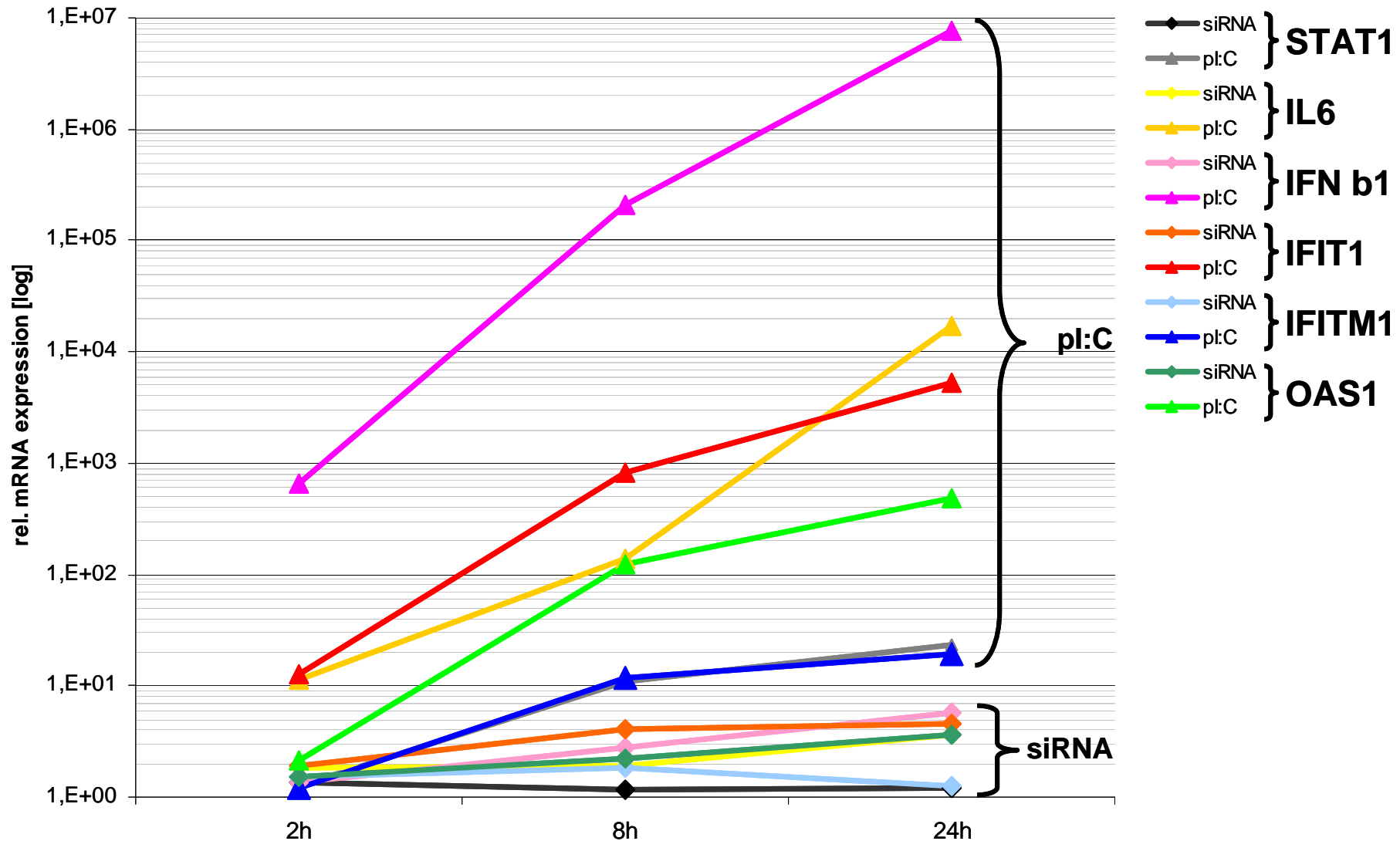
Off-Target Effects: Interferon Pathway



ds RNA of >30 bp activates global toxicity



Off-Target Effects: No Induction of Interferon-regulated genes by siRNAs in MCF-7 cells

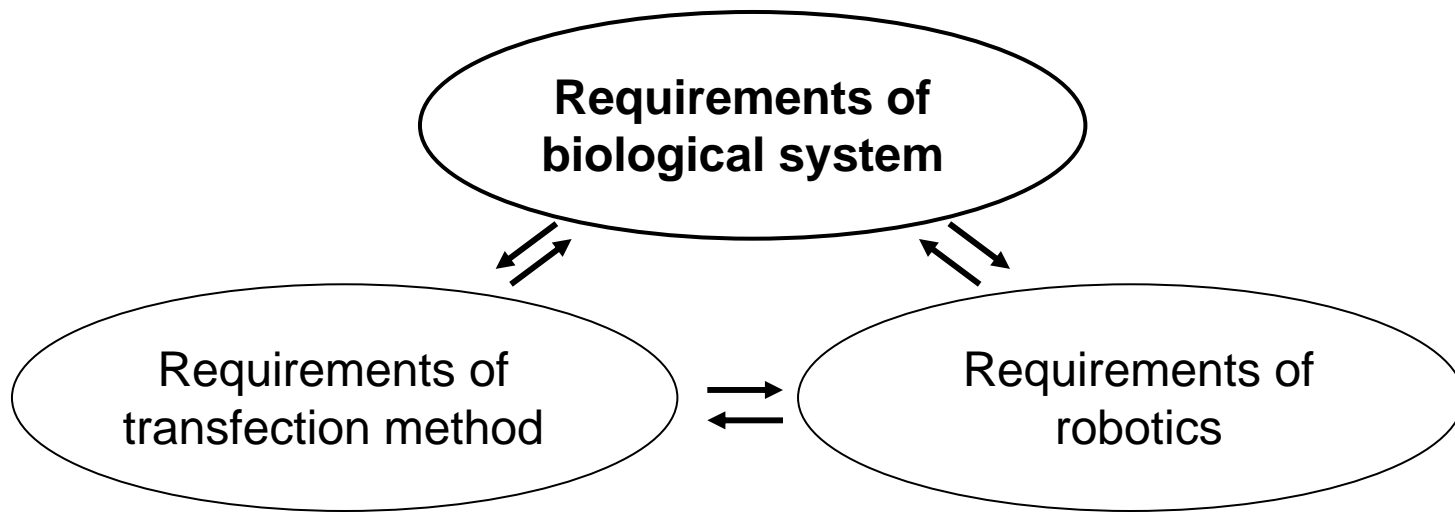


Sequence-specific off-target effects/microRNA effects:

- Careful siRNA design
- Avoiding potential microRNA binding sites

Non-sequence-specific off-target effects:

- Low siRNA concentrations
- Optimized transfection conditions
- Interferon motif avoidance



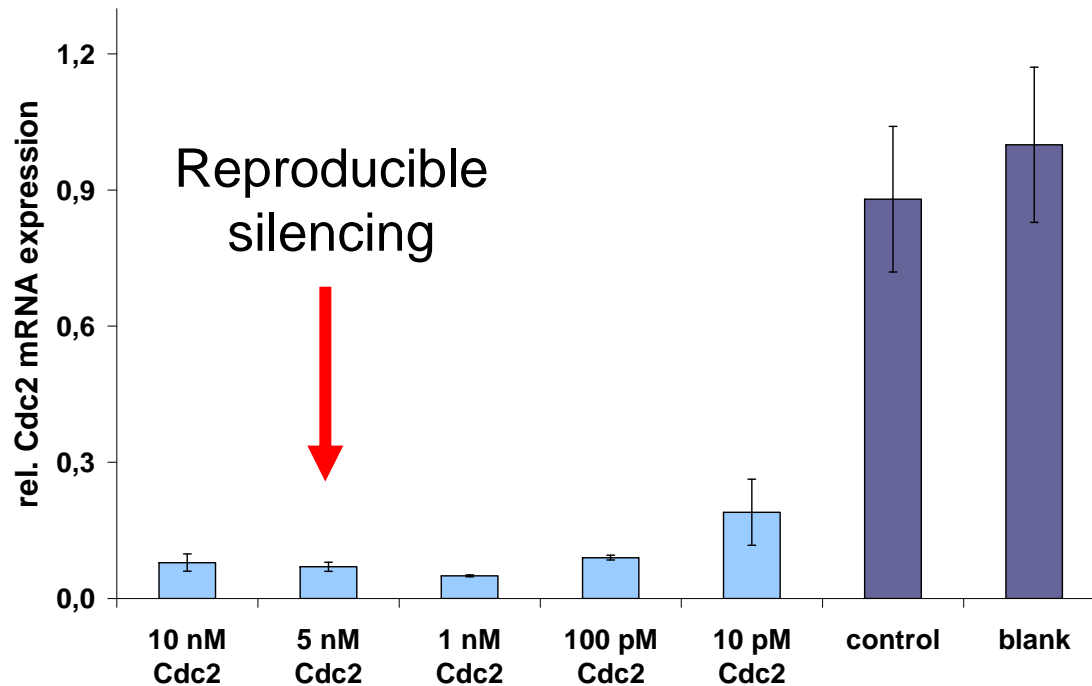
Transfection method:

- High efficiency
- Low cytotoxicity/ low off-target effect
- Transfection of primary cells
- Simple & robust protocol = automatable
- Easy to optimize

⇒ **HiPerFect Transfection Reagent**

Concentration of siRNA:

- Aim: minimal siRNA concentration
- Requirement: robust results



■ **SNP avoidance:**

optimized to avoid known single nucleotide polymorphisms (SNPs) using RefSNP database

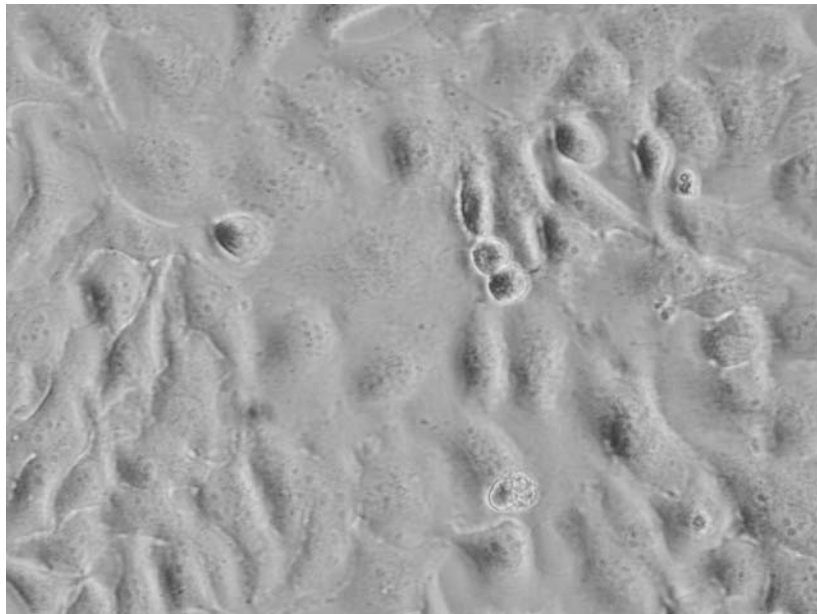
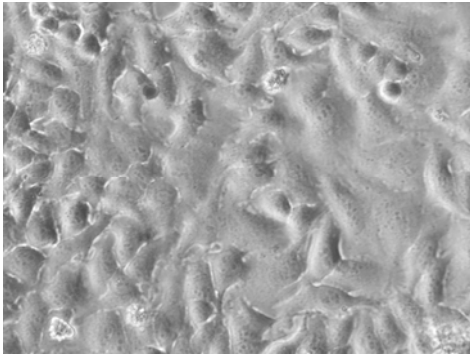
■ **Interferon motif avoidance*:**

screened for multiple sequence motifs known to result in an interferon response

*Hornung et al., Nature Medicine, 2005
Judge et al., Nature Biotech, 2005

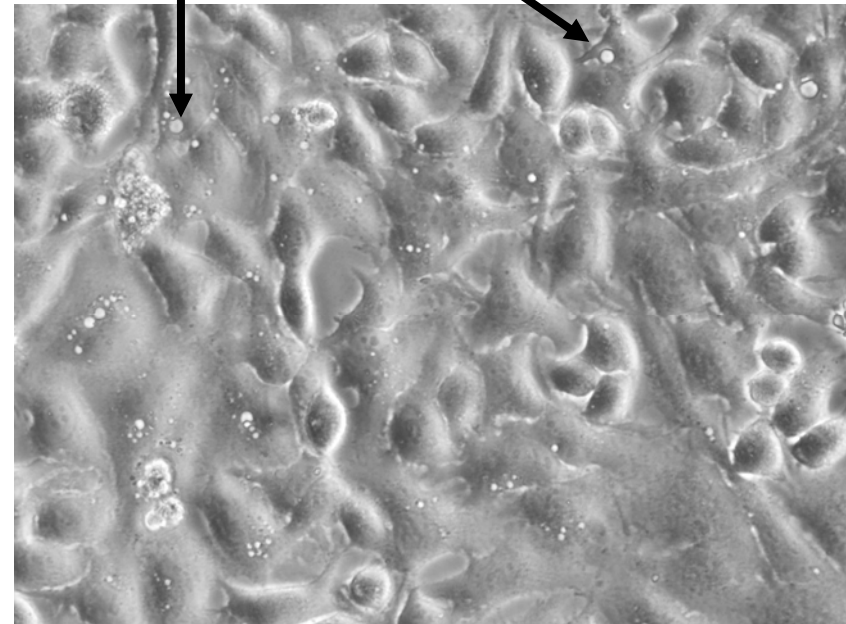
Off-Target Effects: More than Cytotoxicity

Untransf.:



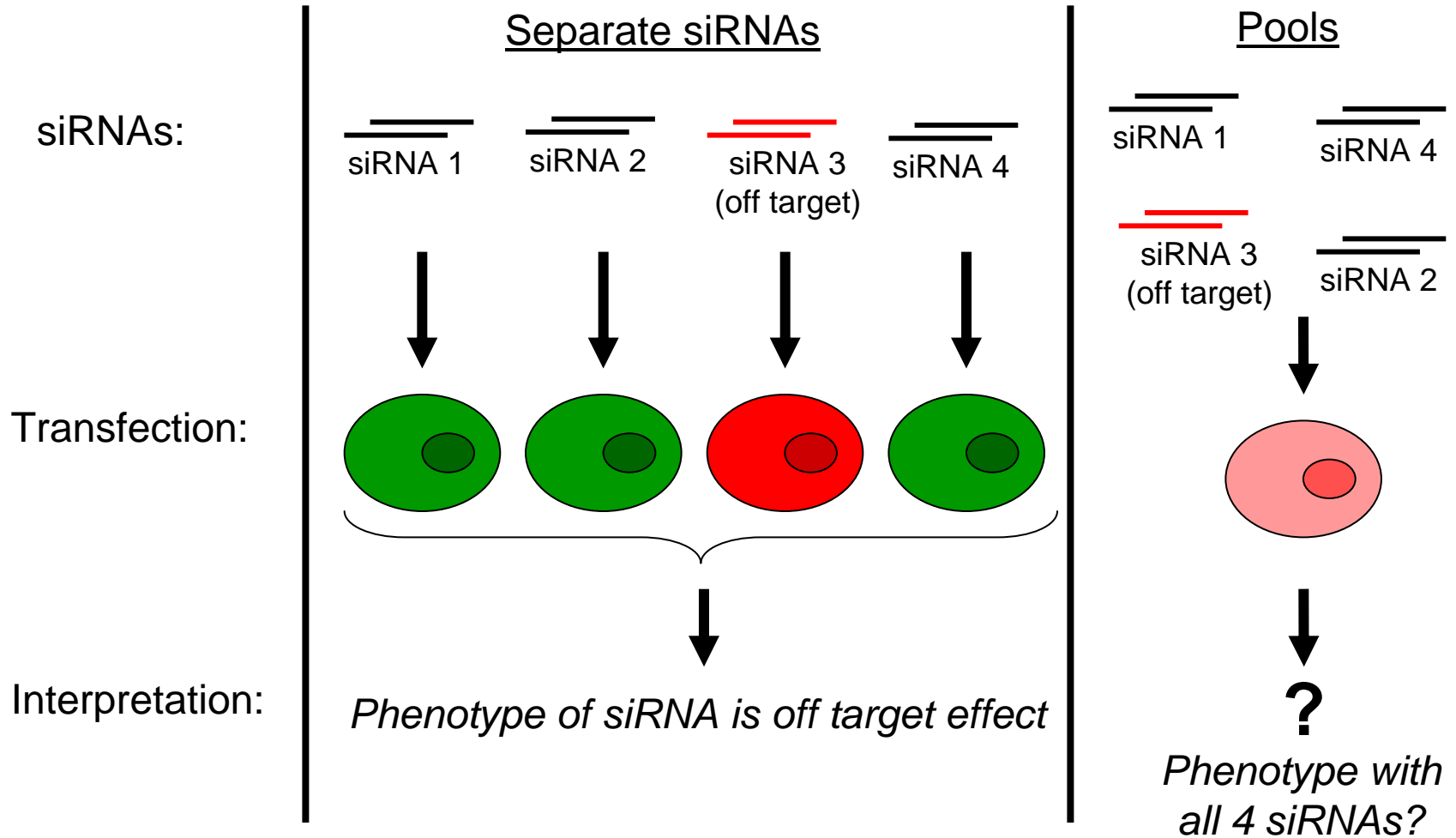
HiPerFect

Vacuoles



Reagent L

Identifying Off-Target Effects: Risks by pooling of siRNA



Dissect an experimental set up as much as possible!

Controls for siRNA transfections

Control	Feature
Untransfected cells	basic activity
Mock transfected cells	transfection reagent effects
Negative control siRNA	non-silencing; general siRNA effect; no homology to any mammalian mRNA; universally applicable
Positive Controls	Functionally validated siRNAs



QIAGEN AllStars RNAi Controls

AllStars RNAi Controls	Description
AllStars Positive Controls	Routine positive controls including a new control siRNA for rat
AllStars Transfection Controls	siRNAs for monitoring transfection efficiency
AllStars Interferon Controls	RT-PCR assays for interferon-induced genes
AllStars Reporter Controls	siRNAs targeting reporter assay genes
AllStars Downstream Controls	RT-PCR assays for quantification of gene expression
AllStars Negative Control siRNA	Thoroughly tested nonsilencing siRNA



AllStars Negative Control siRNA

www.qiagen.com/AllStars

Most thoroughly verified negative control siRNA available

Multiple negative control siRNAs tested for non-specific effects with

- Affymetrix GeneChip Arrays
- Cell-based assays
 - Live-cell nucleic staining
 - Cell number
 - Nucleotide incorporation
 - Live-cell dye exclusion
 - DNA staining
 - RISC-incorporation analysis

AllStars Negative
Control siRNA:

Minimal non-specific
effects – like untreated
cells

Do I want to use siRNA or shRNA? (or both?)

shRNA

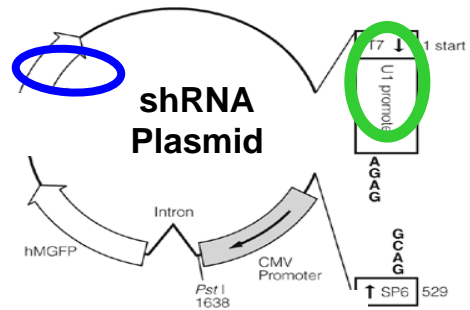
- Ability to use transiently or select for stable cell line
- Renewable & unlimited source of gene knockdown
- Potential to be silenced over time
- Guaranteed to work with 70% Efficiency

siRNA

- Quick transient knockdown
- Unable to select for long term/permanent cells
- Cost-effective for higher gene throughput (different synthesis scales)
- Available in sets (4 siRNA/gene) or 1 design per order
- Able to be modified for longer stability or different types of applications

SureSilencing shRNA Plasmids

**Amp^r:
Propagation**

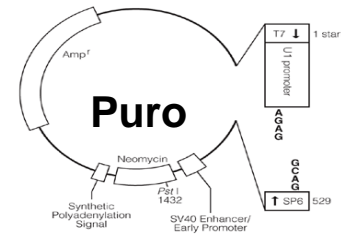
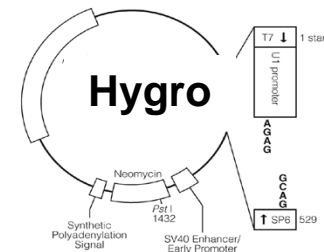
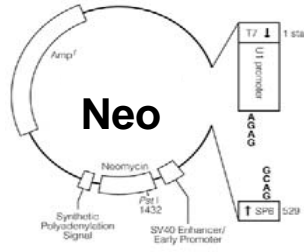
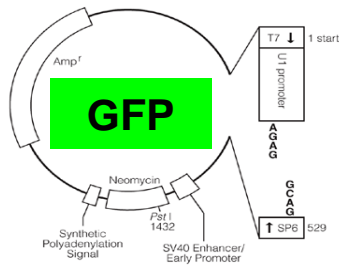


**U1 promoter:
Expression**

Cell Selection

FACS enrichment

Antibiotic-resistance markers: Stable Cell Line Development



4 Designs / Gene – Sequence Targets different regions

- *1st Identify which SureSilencing plasmids with highest gene knock down – 2/4 SureSilencing plasmids GUARANTEED to knock down gene by 70%*

Benefits of SureSilencing shRNA

- Guaranteed success (70% gene knockdown by at least 2 different shRNAs)
- Control for non-specific and off-target effects
- Renewable shRNA resource (life-time supply)
- Multiple selection markers (GFP, Neomycin, Hygromycin, Puromycin)
- Bench validated control shRNAs are available.
- 4 shRNA plasmids and 1 negative control vector

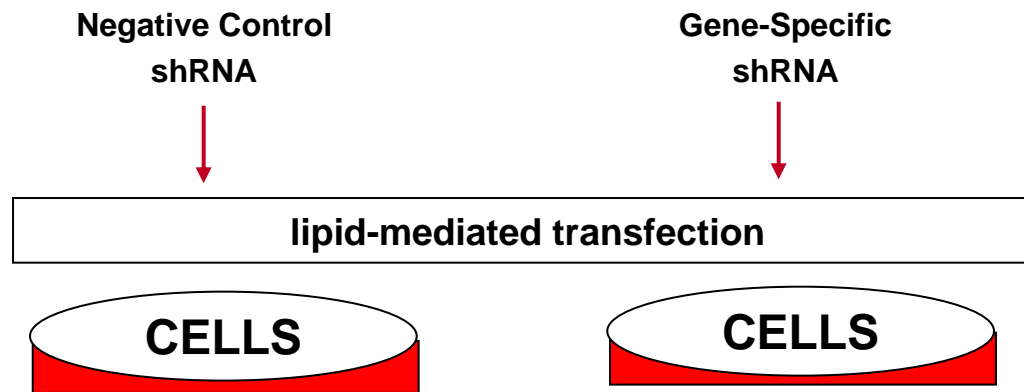
- **Search for shRNA by Gene:**
 - <http://sabiosciences.com/shRNA.php>
- **Search for shRNA by pathway or disease:**
 - <http://sabiosciences.com/ArrayList.php>

Additional materials required:

- Competent *E. coli* cells & other reagents for transformation (LB, ampicillin, plates)
- Plasmid Purification Kit, endotoxin-free
- Lipid-mediated transfection reagent (Attractene) or electroporator
- Real-time PCR reagents for verification of knockdown –
 - cDNA synthesis kit (C-03)
 - RT² Primer Assays
 - RT² SYBR Green Master Mix

SureSilencing shRNA Protocol

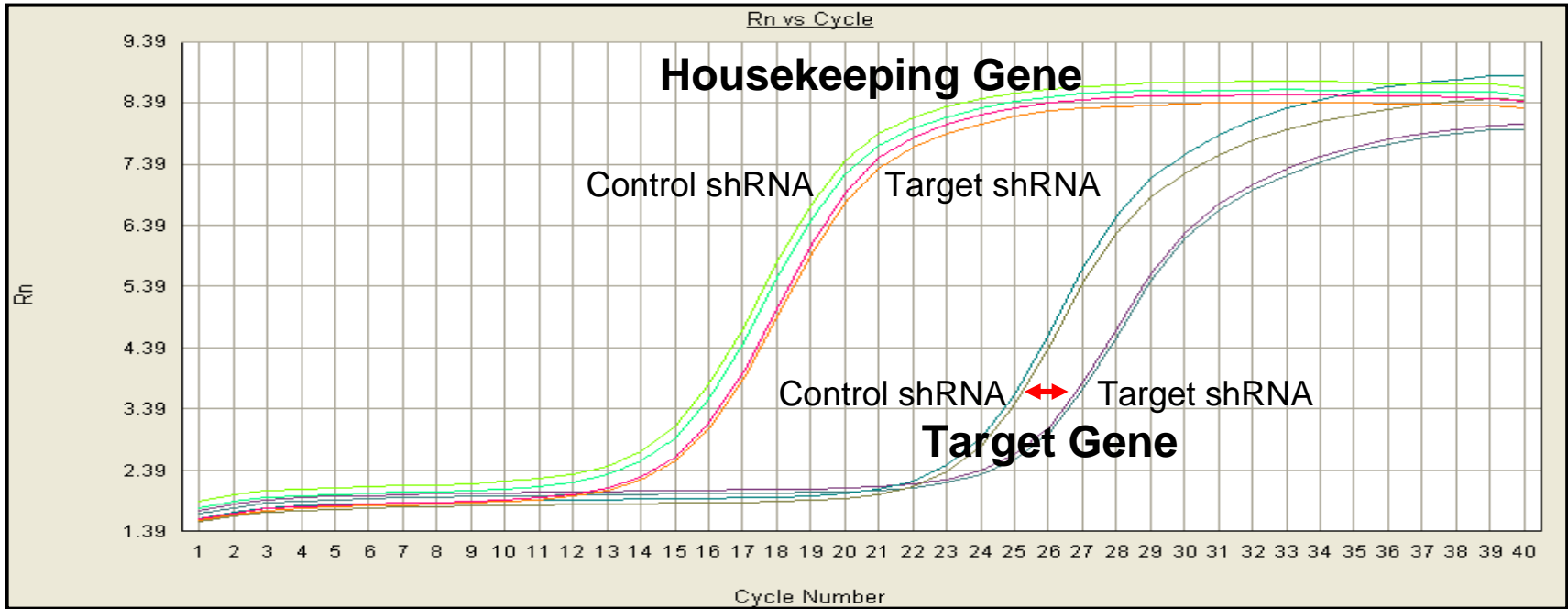
- Transform provided plasmid into competent *E. coli* cells according to manufacturer's instructions.
- Pick colony for large scale bacterial culture and large-scale high-quality transfection-grade plasmid preparation using a kit according to manufacturer's instructions.
- Transfect gene-specific and negative control shRNA plasmids into replicate wells of your cell line of interest:



- **24 to 48 h incubation**
- **GFP-enrich (< 1 day) or**
- **select with antibiotic (~ > 1-2 weeks)**

SureSilencing shRNA Protocol

- Enrich transiently transfected cells by FACS for GFP
OR
- Select for stably transfected cells by selection for antibiotic resistance
- Assay the extent of knock-down by real-time PCR
 - Primers for target gene and housekeeping (control) gene
 - Template from cells transfected with target gene-specific shRNA and negative control shRNA
 - Perform each reaction in triplicate ($n = 3$)
 - $(2 \text{ primer sets}) \times (2 \text{ templates}) \times (3 \text{ replicates}) = 12 \text{ reactions}$
- Perform biochemical, cellular, or molecular assay of choice
 - RT² Profiler PCR Arrays – examine gene expression changes in related pathways

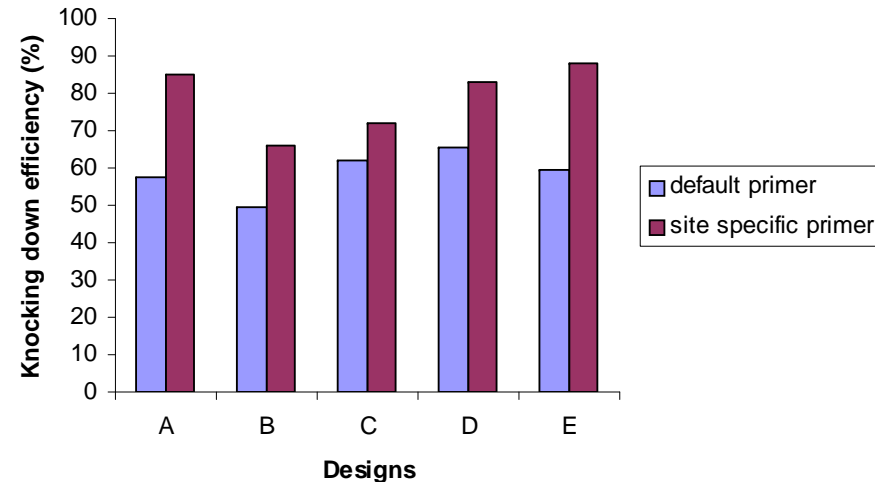


Target gene expression decreases by two threshold cycles, indicating greater than 70% knockdown, and housekeeping gene expression is not altered upon transfection with the target gene shRNA plasmid relative to the control shRNA.

shRNA Knockdown Experiments

- **Validation – at the mRNA level**
 - Real-time PCR
 - Site-specific primer may be necessary for some genes
 - At protein level, knockdown is not always immediately apparent
 - Protein level measurement – Western blot, enzyme activity assay, reporter assay
 - Need to optimize timing

- **Controls**
- **Enrichment**



Negative Controls for shRNA Experiments

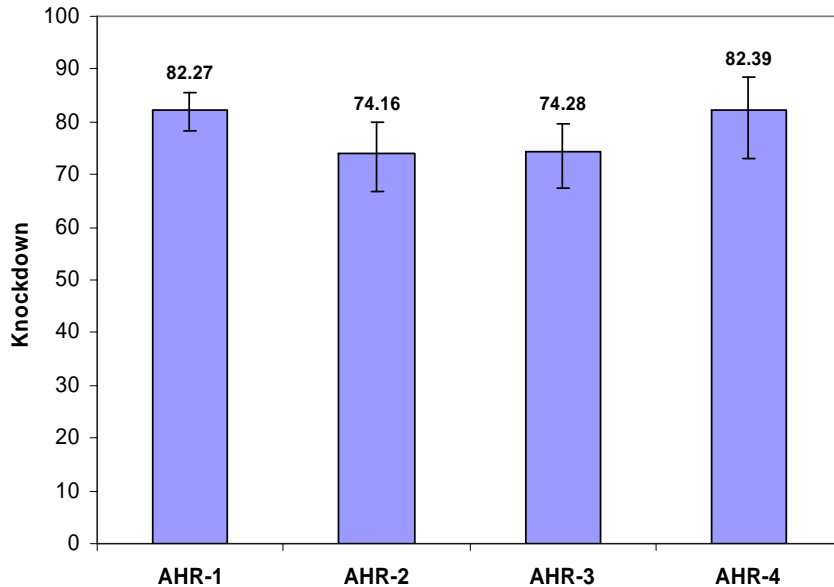
- **Untreated Cells:** Use normal cells in a normal culture condition as a pure background.
- **Mock control for transfection reagent (transient experiment only):** Cells treated with transfection reagent only without any shRNA plasmid DNA. Helps to identify any effect directly from the transfection reagent.
- **Non-Targeting shRNA Control:** Use the same shRNA expression vector that will activate RISC and the RNAi pathway, but does not target any human, mouse or rat genes. This allows for examination of the effects of shRNA transfection and RNAi activation on gene expression. Cells transfected with the non-target shRNA vector will also provide a useful reference for interpretation of knockdown. **This negative control is provided with each shRNA plasmid set.**

FACS-Based Enrichment for GFP-Expressing Cells

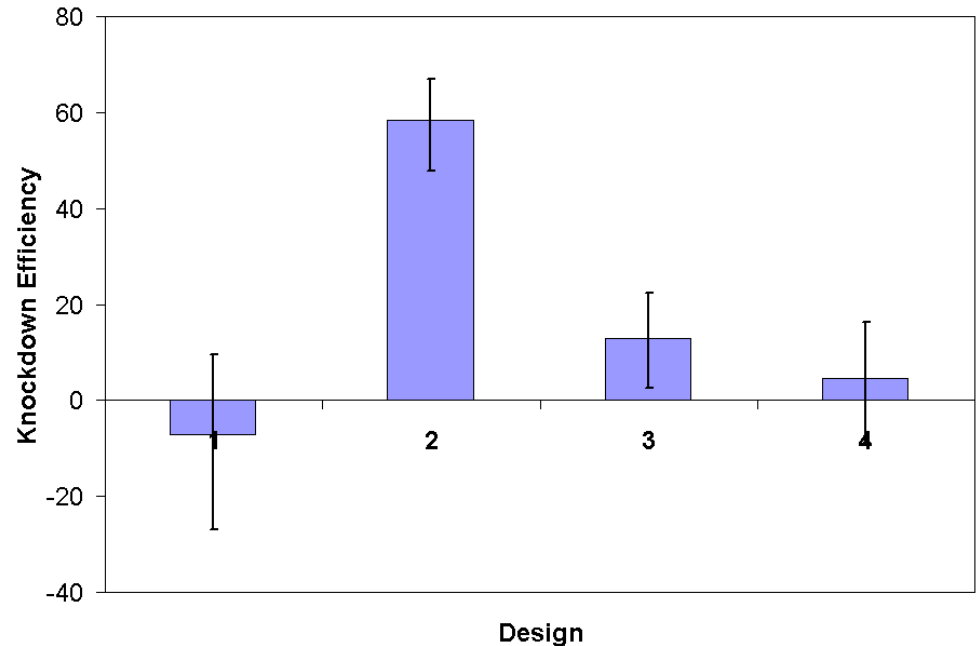
Percent Knockdown	Pre-Sorted Population (%) Knockdown	Sorted Population(%) Knockdown
PRKCA Protein Kinase C alpha	37	<u>71.8 (69.7, 73.8)</u>
TP53 Tumor protein p53	52	<u>70.8 (68.4, 73.0)</u>

Transient transfection may have lower efficiency in some cell lines. Unsorted cells will exhibit lower knock-down due to a large population of untransfected cells. Sorting will remove the untransfected cells and enrich the population, thus providing a true measurement of knockdown.

Antibiotic selection strategy-potential challenge when using pooled population



High efficiency transient transfection

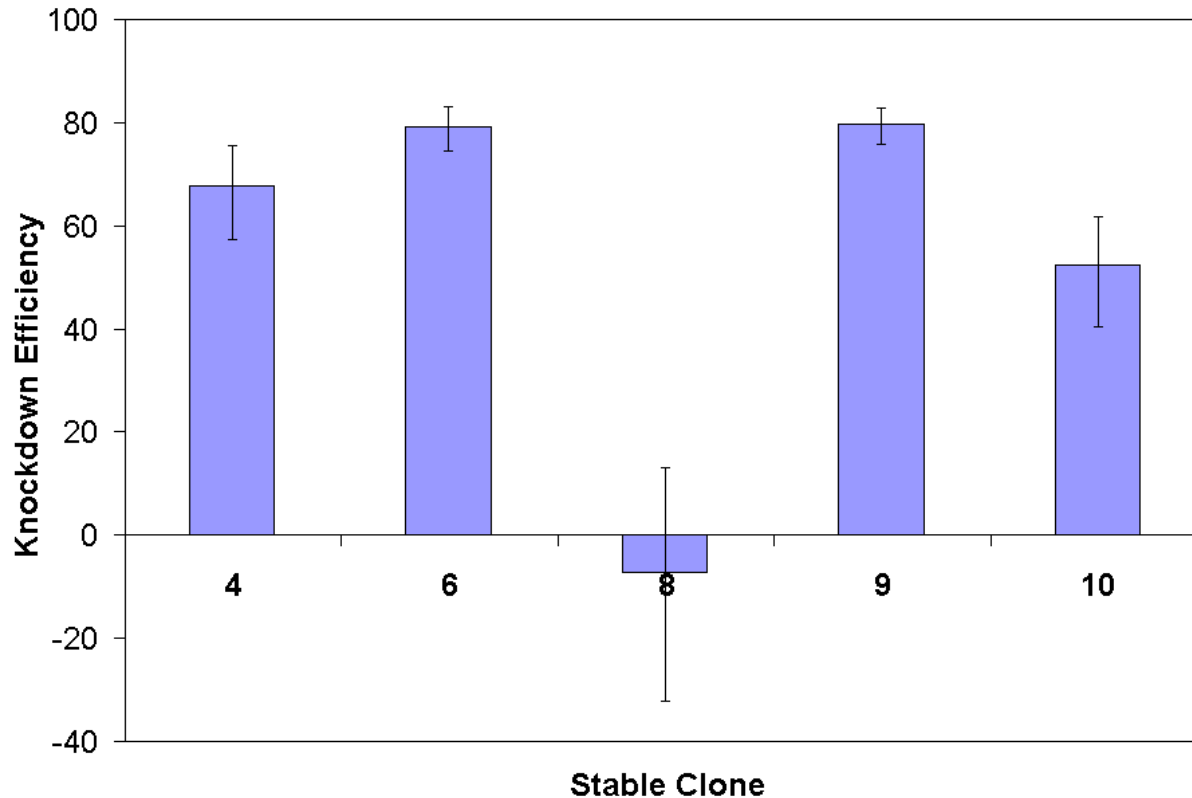


Selection using entire pool

- Initial stably antibiotic selected whole pool population appears to fail
- Random integration sites affect shRNA expression and percent KD
- Average KD of all integration sites seen – some better than others

SureSilencing shRNA Selection

Individual Stably Selected Clones



Clone cells stably transfected with two best designs and selected by limited dilution

Re-validate clones: Two out of five tested now successful

Citations Using SureSilencing shRNA Plasmids

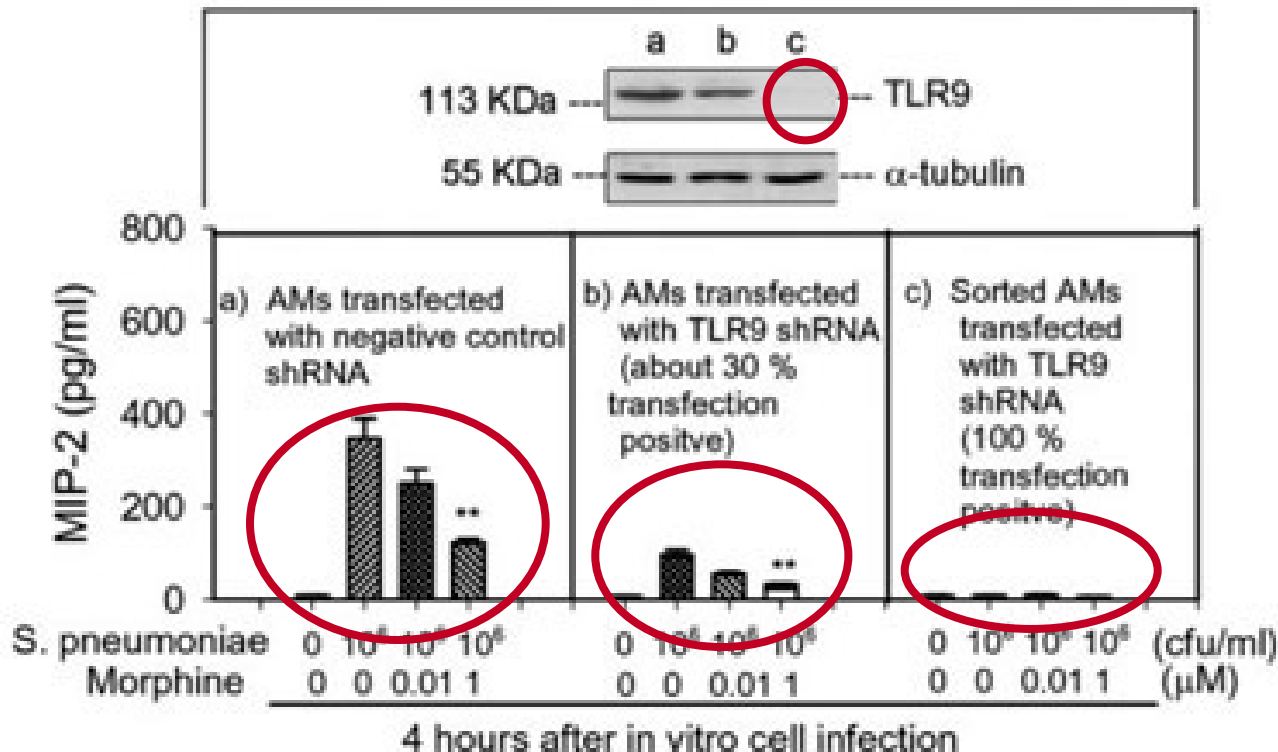
- Cancer** Baritaki S, Huerta-Yepey S, Sakai T, Spandidos DA, Bonavida B. Chemotherapeutic drugs sensitize cancer cells to TRAIL-mediated apoptosis: up-regulation of DR5 and inhibition of Yin Yang 1. *Mol Cancer Ther.* 2007 Apr;6(4):1387-99. [PUBMED](#) Demorrow S, Francis H, Gaudio E, Ueno Y, Venter J, Onori P, Franchitto A, Vaculin B, Vaculin S, Alpini G. Anandamide inhibits cholangiocyte hyperplastic proliferation via activation of thioredoxin 1/redox factor 1 and AP-1 activation. *Am J Physiol Gastrointest Liver Physiol.* 2007 Dec 20 [Epub ahead of print] [PUBMED](#) Demorrow S, Glaser S, Francis H, Venter J, Vaculin B, Vaculin S, Alpini G. Opposing actions of endocannabinoids on cholangiocarcinoma growth: Recruitment of fas and fas ligand to lipid rafts. *J Biol Chem.* 2007 Apr 27;282(17):13098-113. Epub 2007 Feb 28. [PUBMED](#) Dhakshinamoorthy S, Sridharan SR, Li L, Ng PY, Boxer LM, Porter AG. Protein/DNA arrays identify nitric oxide-regulated cis-element and trans-factor activities some of which govern neuroblastoma cell viability. *Nucleic Acids Res.* 2007;35(16):5439-51. Epub 2007 Aug 15. [PUBMED](#) Dimple C, Nair SS, Rajhans R, Pitcheswara PR, Liu J, Balasenthil S, Le XF, Burow ME, Auersperg N, Tekmal RR, Broaddus RR, Vadlamudi RK. Role of PELP1/MNAR signaling in ovarian tumorigenesis. *Cancer Res.* 2008 Jun 15;68(12):4902-9. [PUBMED](#) Guo Y, Xie J, Rubin E, Tang YX, Lin F, Zi X, Hoang BH, Frzb, a secreted Wnt antagonist, decreases growth and invasiveness of fibrosarcoma cells associated with inhibition of Met signaling. *Cancer Res.* 2008 May 1;68(9):3350-60. [PUBMED](#) Horak CE, Lee JH, Elkahloun AG, Boissan M, Dumont S, Maga TK, Arnaud-Dabernat S, Palmieri D, Stetler-Stevenson WG, Lacombe ML, Meltzer PS, Steeg PS. Nm23-H1 suppresses tumor cell motility by down-regulating the lysophosphatidic acid receptor EDG2. *Cancer Res.* 2007 Aug 1;67(15):7238-46. [PUBMED](#) McFate T, Mohyeldin A, Lu H, Thakar J, Henriques J, Halim ND, Wu H, Schell MJ, Tsang TM, Teahan O, Zhou S, Califano JA, Jeoung NH, Harris RA, Verma A. Pyruvate dehydrogenase complex activity controls metabolic and malignant phenotype in cancer cells. *J Biol Chem.* 2008 Jun 9. [Epub ahead of print] [PUBMED](#) McGowan PM, Ryan BM, Hill AD, McDermott E, O'Higgins N, Duffy MJ. ADAM-17 expression in breast cancer correlates with variables of tumor progression. *Clin Cancer Res.* 2007 Apr 15;13(8):2335-43. [PUBMED](#) Rajhans R, Nair HB, Nair SS, Cortez V, Ikuko K, Kirma NB, Zhou D, Holden AE, Brann DW, Chen S, Tekmal RR, Vadlamudi RK. Modulation of in situ Estrogen Synthesis by PELP1: Potential ER Autocrine Signaling Loop in Breast Cancer Cells. *Mol Endocrinol.* 2007 Dec 13 [Epub ahead of print] [PUBMED](#) Tirado OM, Mateo-Lozano S, Villar J, Dettin LE, Llort A, Gallego S, Ban J, Kovar H, Notario V. Caveolin-1 (CAV1) is a target of EWS/FLI-1 and a key determinant of the oncogenic phenotype and tumorigenicity of Ewing's sarcoma cells. *Cancer Res.* 2006 Oct 15;66(20):9937-47. [PUBMED](#) Zhao S, Venkatasubbarao K, Lazor JW, Sperry J, Jin C, Cao L, Freeman JW. Inhibition of STAT3 Tyr705 phosphorylation by Smad4 suppresses transforming growth factor beta-mediated invasion and metastasis in pancreatic cancer cells. *Cancer Res.* 2008 Jun 1;68(11):4221-8. [PUBMED](#)
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- Immunology** Lawson BR, Manenkova Y, Ahamed J, Chen X, Zou JP, Baccala R, Theofilopoulos AN, Yuan C. Inhibition of transmethylation down-regulates CD4 T cell activation and curtails development of autoimmunity in a model system. *J Immunol.* 2007 Apr 15;178(8):5366-74. [PUBMED](#) Wang J, Barke RA, Charboneau R, Schwendener R, Roy S. Morphine Induces Defects in Early Response of Alveolar Macrophages to Streptococcus pneumoniae by Modulating TLR9-NF-(kappa)B Signaling. *J Immunol.* 2008 Mar 1;180(5):3594-600. [PUBMED](#)
- Neuroscience** Uo T, Kinoshita Y, Morrison RS. Apoptotic actions of p53 require transcriptional activation of PUMA and do not involve a direct mitochondrial/cytoplasmic site of action in postnatal cortical neurons. *J Neurosci.* 2007 Nov 7;27(45):12198-210. [PUBMED](#)
- Signal Transduction** Ciccone NA, Lacza CT, Hou MY, Gregory SJ, Kam KY, Xu S, Kaiser UB. A Composite Element that Binds Basic Helix Loop Helix and Basic Leucine Zipper Transcription Factors Is Important for GnRH Regulation of the FSH(beta) Gene. *Mol Endocrinol.* 2008 Jun 11. [Epub ahead of print] [PUBMED](#) Xue M, Campbell D, Jackson CJ. Protein C is an autocrine growth factor for human skin keratinocytes. *J Biol Chem.* 2007 May 4;282(18):13610-6. Epub 2007 Feb 9. [PUBMED](#)
- Stem Cells** Guo Y, Mantel C, Hromas RA, Broxmeyer HE. Oct-4 is critical for survival/antiapoptosis of murine embryonic stem cells subjected to stress: effects associated with Stat3/survivin. *Stem Cells.* 2008 Jan;26(1):30-4. Epub 2007 Oct 11. [PUBMED](#) Liou JY, Ellent DP, Lee S, Goldsby J, Ko BS, Matijevic N, Huang JC, Wu KK. Cyclooxygenase-2-derived prostaglandin e2 protects mouse embryonic stem cells from apoptosis. *Stem Cells.* 2007 May;25(5):1096-103. Epub 2007 Jan 18. [PUBMED](#) Wang XY, Yin Y, Yuan H, Sakamaki T, Okano H, Glazer RI. Musashi1 modulates mammary progenitor cell expansion through proliferin-mediated activation of the Wnt and Notch pathways. *Mol Cell Biol.* 2008 Jun;28(11):3589-99. Epub 2008 Mar 24. [PUBMED](#)

•Website: http://www.sabiosciences.com/support_publication.php

SureSilencing shRNA– Published Results

TLR9 Necessary for Induction of Immune Response

~100% Knockdown in Macrophage Cells

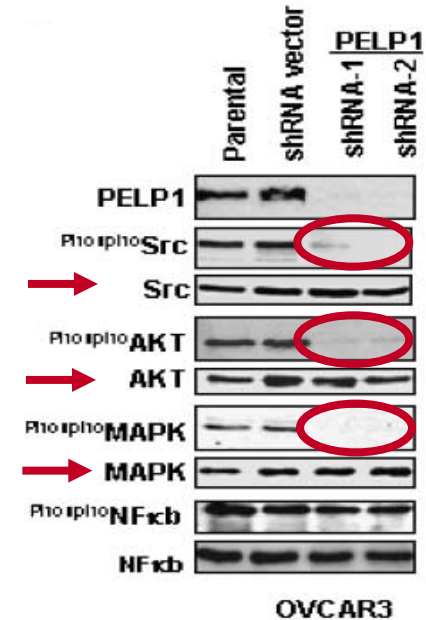
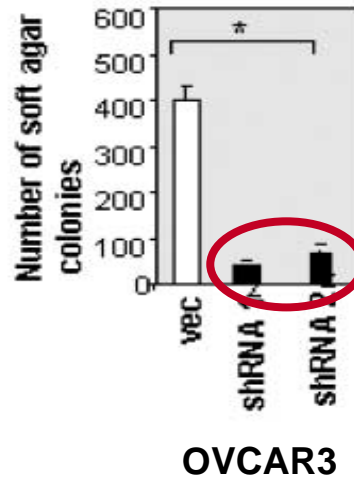
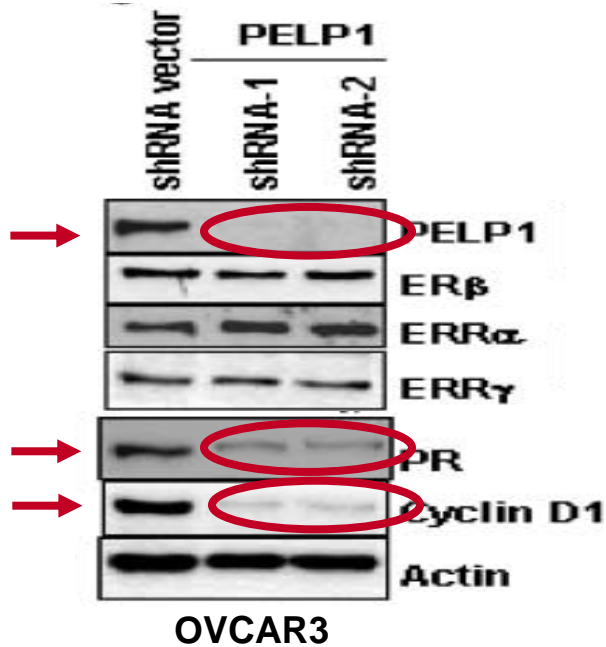


AM = Alveolar Macrophage

Wang J, Barke RA, Charboneau R, Schwendener R, Roy S. 2008. Morphine induces defects in early response of alveolar macrophages to *Streptococcus pneumoniae* by modulating TLR9-NF-kappaB signaling. *J. Immunology*. 180:3594-3600. (Reprinted under copyright permission from the Journal of Immunology.)

PELP1 Contributes to Cellular Proliferation Signaling

~100% knockdown in OVCAR3 cells



Dimple C, Nair SS, Rajhans R, Pitcheswara PR, Liu J, Balasenthil S, Le XF, Burow ME, Auersperg N, Tekmal RR, Broaddus RR, Vadlamudi RK. 2008. Role of PELP1/MNAR Signaling in Ovarian Tumorigenesis. *Cancer Research*. 68: 4902-4909. (Reprinted Under Copyright permission from AACR)

■ Introduction

- RNA Interference: Why use RNAi?
- How does siRNA and shRNA work?
- Challenges
- Solutions

■ siRNA

- Types of siRNA available from QIAGEN
- Protocol/Optimizations
- Research Applications (transient screening, high throughput)

■ shRNA

- shRNA plasmids: maps, features and utility
- Optimizations
- Research Applications (permanent knockdown or transient selection)

■ Validation of RNAi Experiments]

■ Summary

- Pilot Study Offer for shRNA and Gene Expression

- Select your siRNA sequence carefully (Algorithm development)
- Minimize the amount of siRNA (Off-Target Effect minimization)
- Optimize the transfection and culture conditions
- Employ appropriate negative and positive controls



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