GeneCopoeia CRISPR Genome Editing Technology

Presenter:

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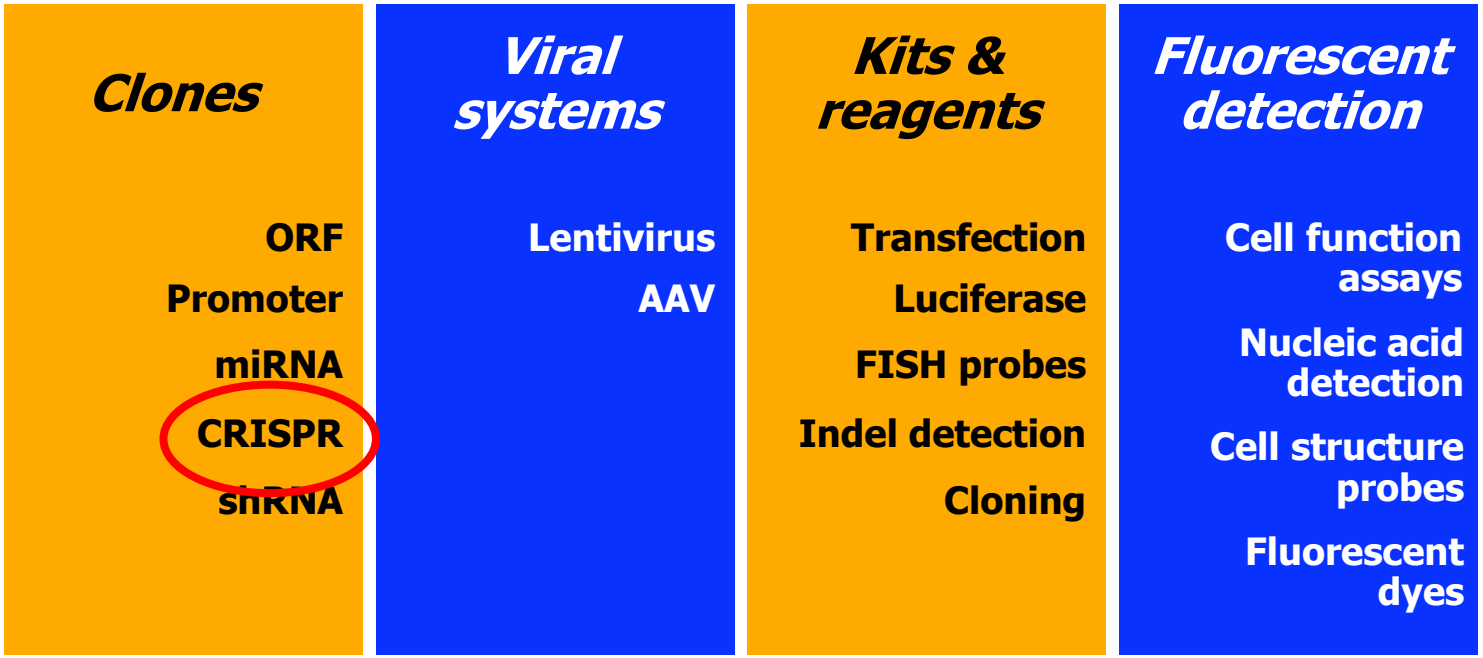
GeneCopoeia, Inc.

January 25, 2017

GeneCopoeia products & services

Functional Genomics & Cell Biology



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Outline

- Genome editing: Technologies
- Applications for genome editing
- How GeneCopoeia can help you with genome editing

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CRISPR or RNAi?

Knock down vs. Knock out

Method	Change expression level	Knock down	Knock out	Change genetic code
CRISPR	✓		✓	✓
RNAi	✓	✓		

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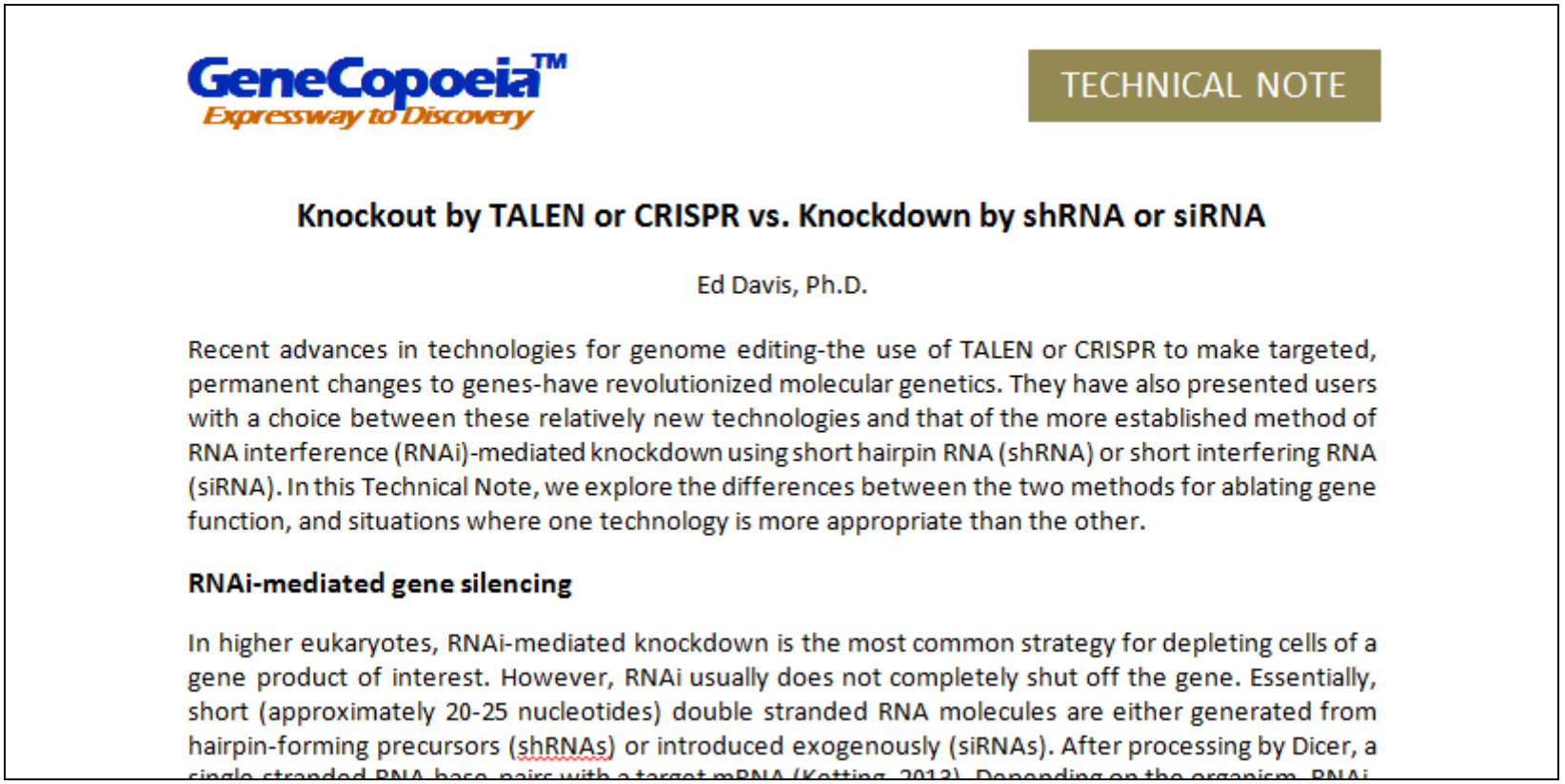
Other techniques of gene manipulation

GeneCopoeia Technical Note: Knockdown vs. Knockout



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TECHNICAL NOTE

Knockout by TALEN or CRISPR vs. Knockdown by shRNA or siRNA

Ed Davis, Ph.D.

Recent advances in technologies for genome editing-the use of TALEN or CRISPR to make targeted, permanent changes to genes-have revolutionized molecular genetics. They have also presented users with a choice between these relatively new technologies and that of the more established method of RNA interference (RNAi)-mediated knockdown using short hairpin RNA (shRNA) or short interfering RNA (siRNA). In this Technical Note, we explore the differences between the two methods for ablating gene function, and situations where one technology is more appropriate than the other.

RNAi-mediated gene silencing

In higher eukaryotes, RNAi-mediated knockdown is the most common strategy for depleting cells of a gene product of interest. However, RNAi usually does not completely shut off the gene. Essentially, short (approximately 20-25 nucleotides) double stranded RNA molecules are either generated from hairpin-forming precursors (shRNAs) or introduced exogenously (siRNAs). After processing by Dicer, a

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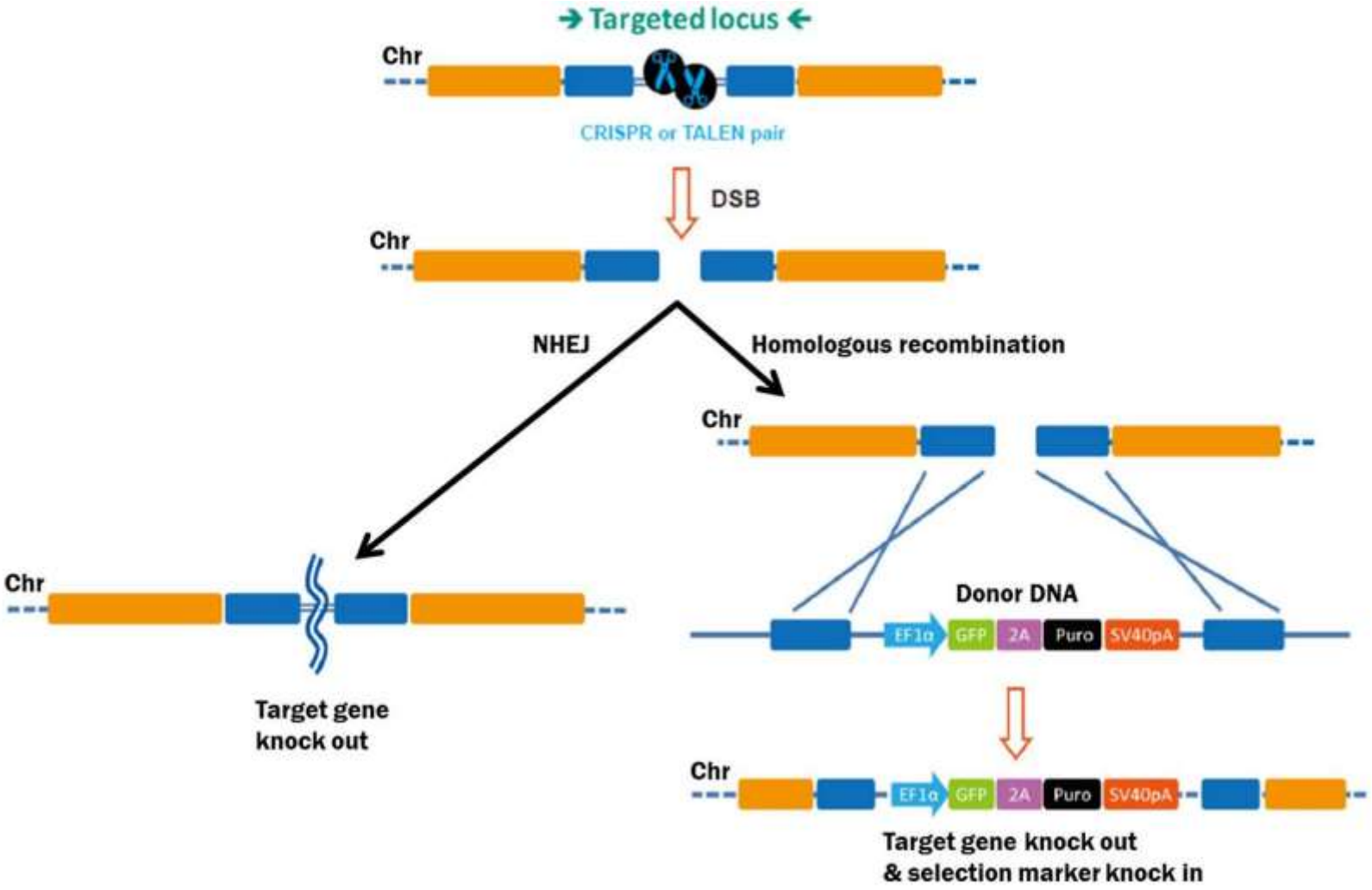
Targeted DNA editing by DSB induction



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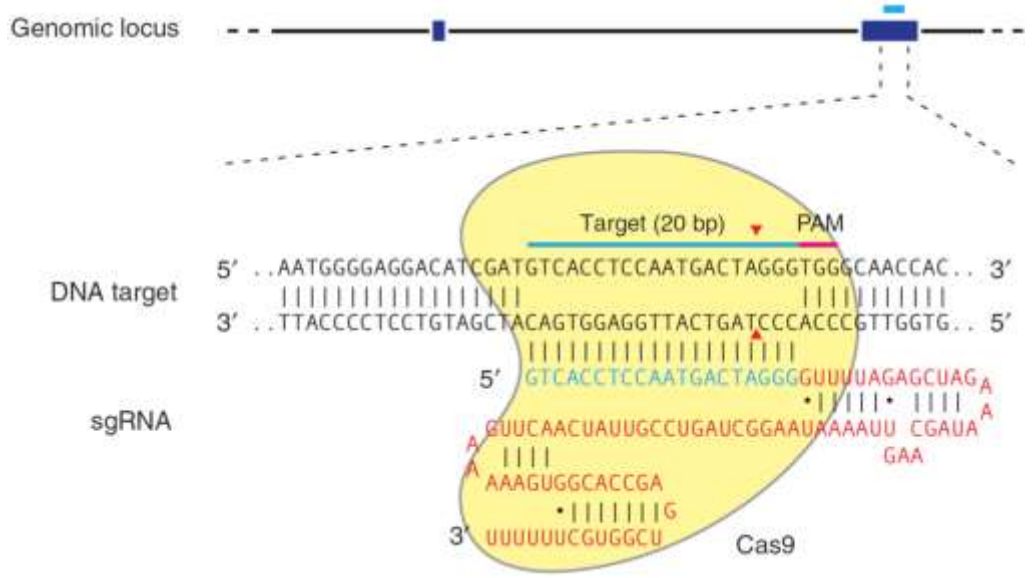
CRISPR genome editing technology

CRISPR-Cas9: RNA-guided endonuclease



Ran, et al. (2013). Nature Protocols 8, 2281

- 20 nt single guide RNA (sgRNA) guides Cas9 nuclease to target site.
- Requires NGG “PAM” site immediately downstream of sgRNA target sequence.
- Cas9-RNA complex makes DSB 3-4 nt upstream of PAM.
- Target almost any gene in any cell

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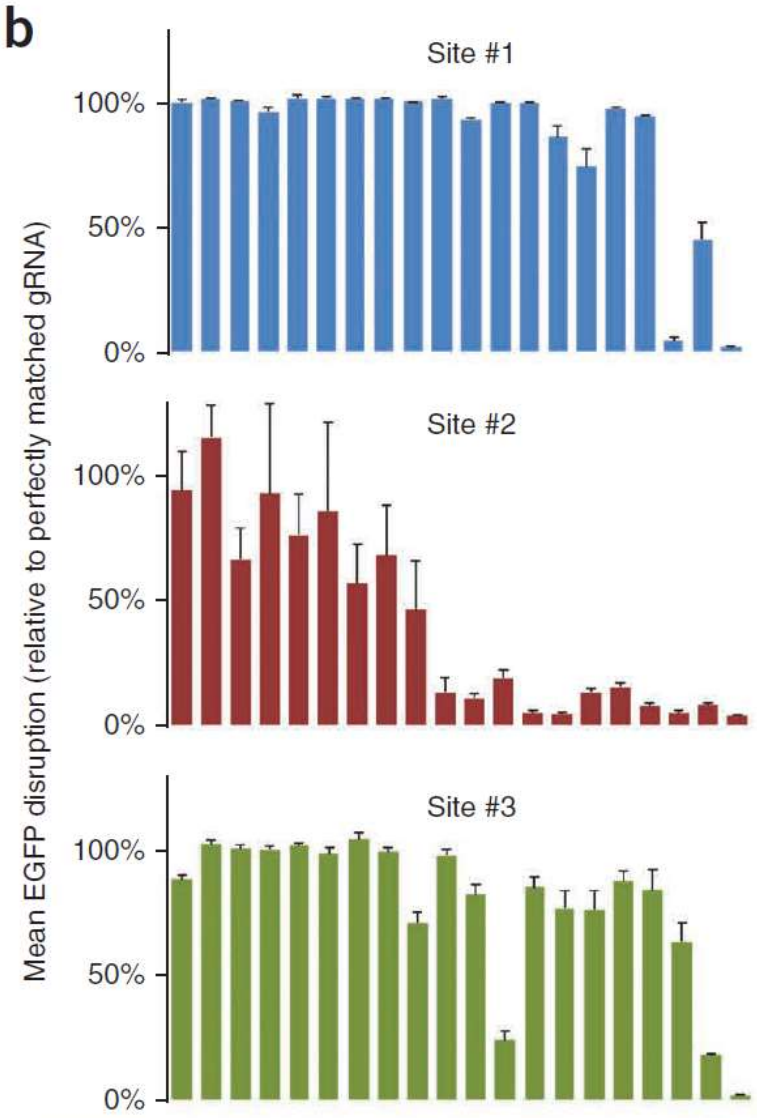
CRISPR-Cas9: Specificity



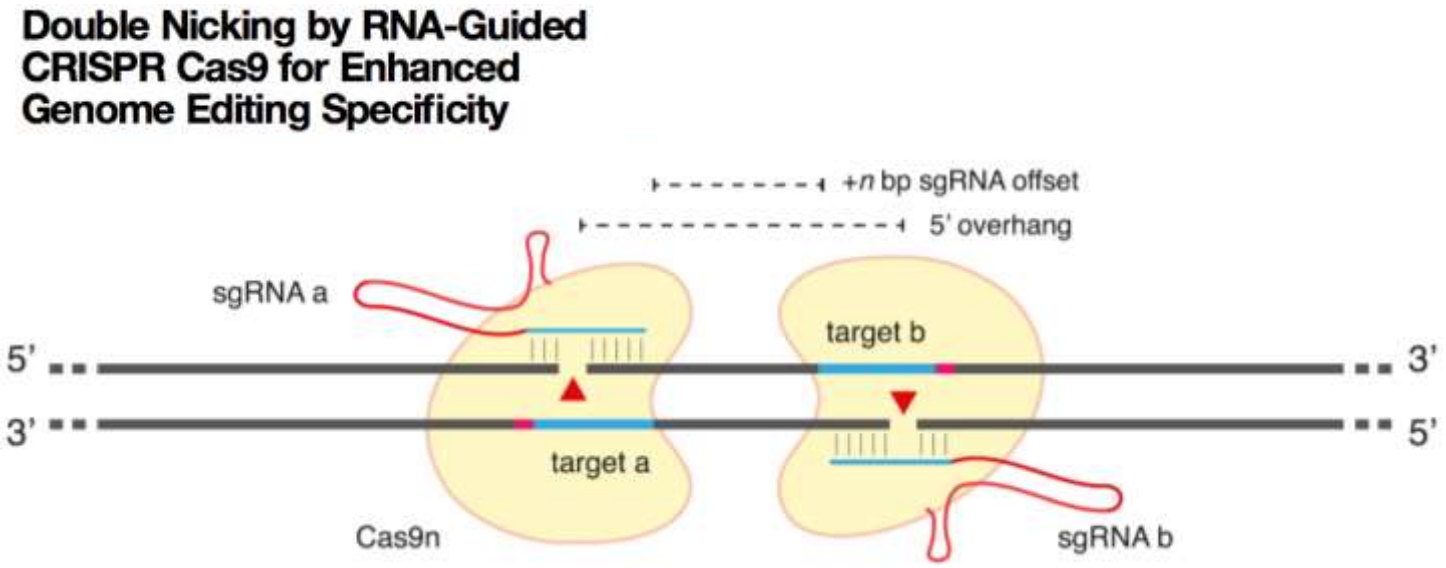
High-frequency off-target mutagenesis induced by CRISPR-Cas nucleases in human cells

Yanfang Fu[1–4], Jennifer A Foden[1–3], Cyd Khayter[1–3], Morgan L Maeder[1–3,5], Deepak Reyon[1–4], J Keith Joung[1–5] & Jeffry D Sander[1–4]

- Showed that some sgRNAs with single, double, and even up to 5 transversion mismatches could still direct Cas9 to mutate EGFP.
- Found that for 4 of 6 tested sgRNAs, evidence of off-target mutagenesis (5.6% -125% of the intended targets).

Fu, et al. (2013). Nature Biotech. 21, 822

CRISPR-Cas9: Specificity

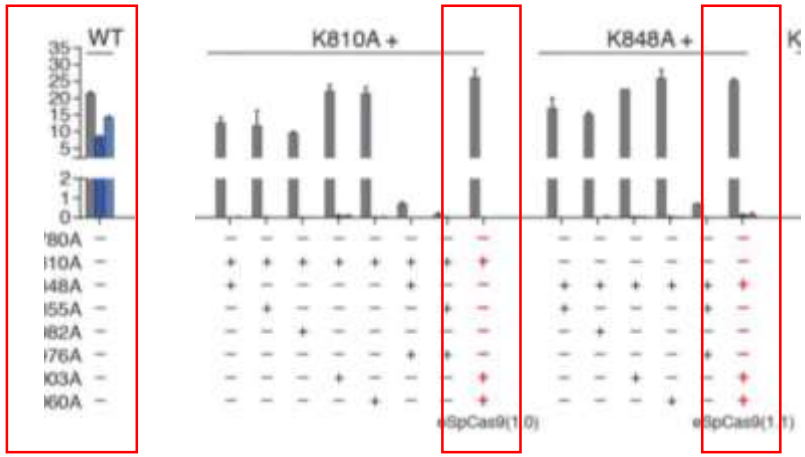


Ran, et al. (2013). Cell 154, 1380

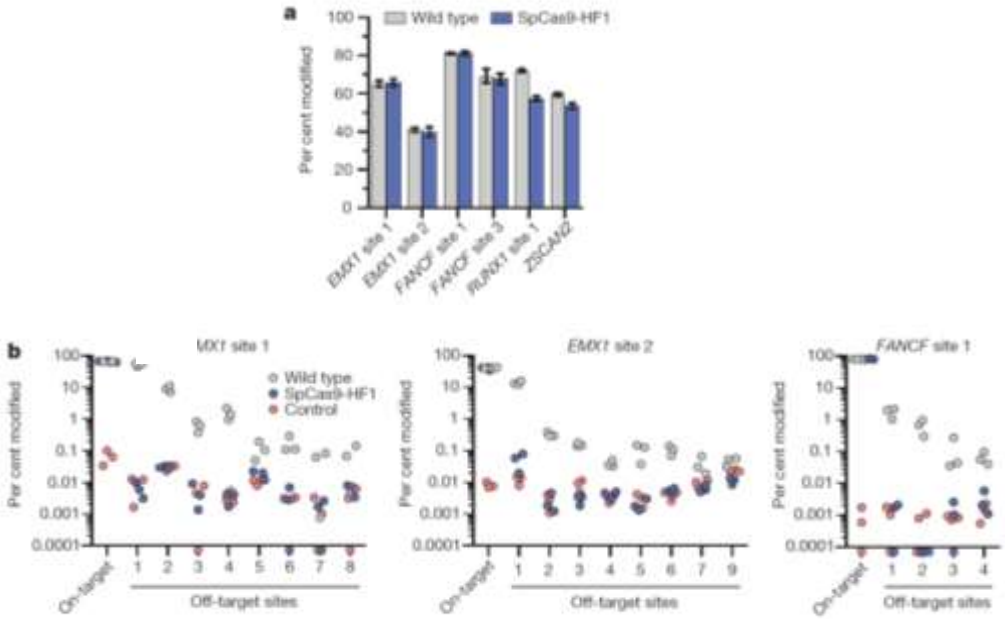
- Cas9 D10A "nickase" mutant creates single-strand nicks instead of DSBs
- Off-target nicks repaired by high-fidelity base excision repair
- Permits ability to generate dimer-like chimeric endonuclease, similar to TALEN. 2 nicks will create a DSB
- Dramatically (50x-1,500x) reduces incidence of off-target effects

CRISPR-Cas9: Specificity

Cas9 point mutants



Slaymaker, et al. (2015). Science



Kleinstiver, et al. (2016). Nature **529**, 490

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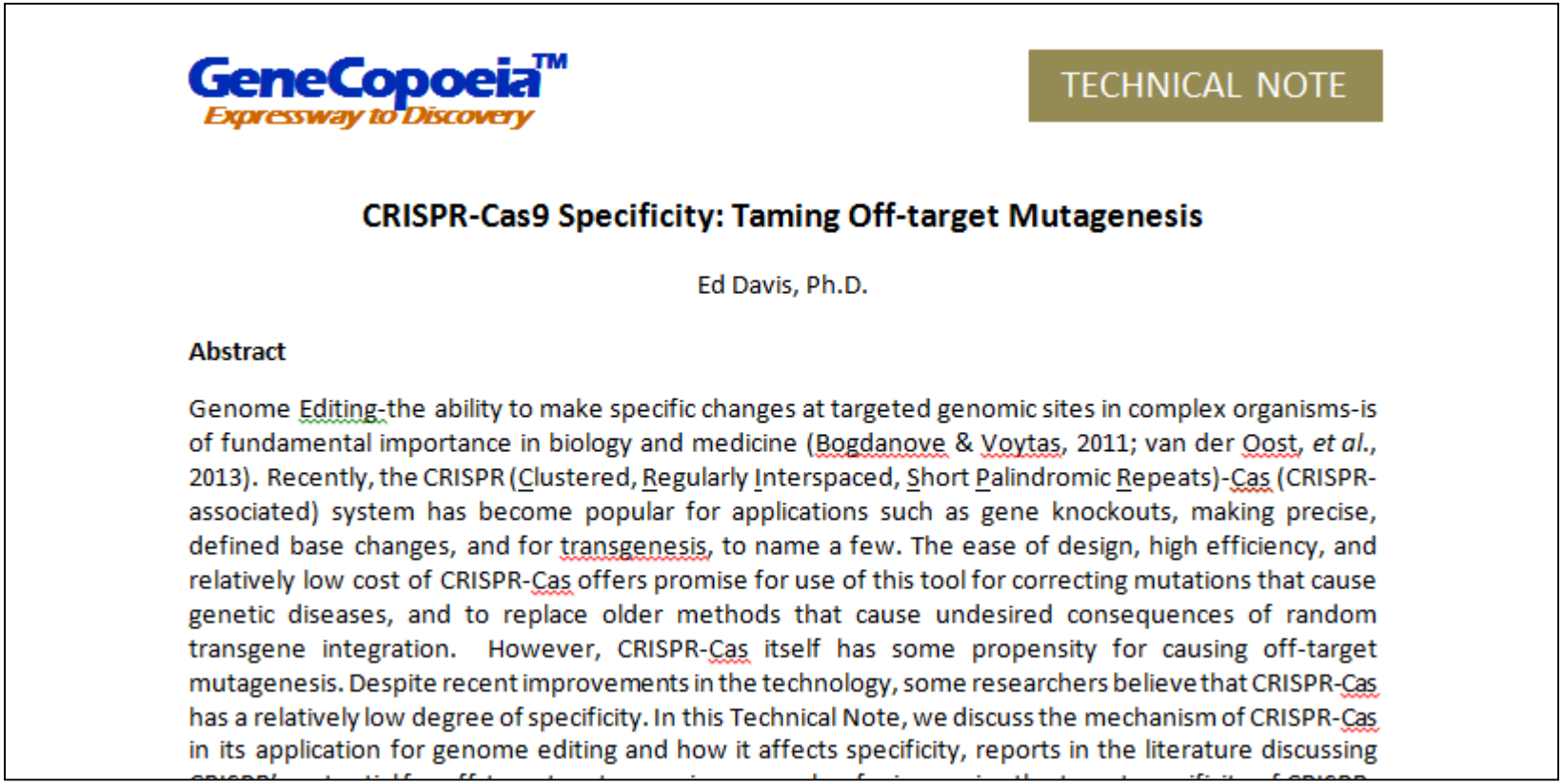
CRISPR-Cas9: Specificity

GeneCopoeia Technical Note: CRISPR specificity



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TECHNICAL NOTE

CRISPR-Cas9 Specificity: Taming Off-target Mutagenesis

Ed Davis, Ph.D.

Abstract

Genome Editing-the ability to make specific changes at targeted genomic sites in complex organisms-is of fundamental importance in biology and medicine (Bogdanove & Voytas, 2011; van der Oost, *et al.*, 2013). Recently, the CRISPR (Clustered, Regularly Interspaced, Short Palindromic Repeats)-Cas (CRISPR-associated) system has become popular for applications such as gene knockouts, making precise, defined base changes, and for transgenesis, to name a few. The ease of design, high efficiency, and relatively low cost of CRISPR-Cas offers promise for use of this tool for correcting mutations that cause genetic diseases, and to replace older methods that cause undesired consequences of random transgene integration. However, CRISPR-Cas itself has some propensity for causing off-target mutagenesis. Despite recent improvements in the technology, some researchers believe that CRISPR-Cas has a relatively low degree of specificity. In this Technical Note, we discuss the mechanism of CRISPR-Cas in its application for genome editing and how it affects specificity, reports in the literature discussing

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Outline

- Genome editing: Technologies
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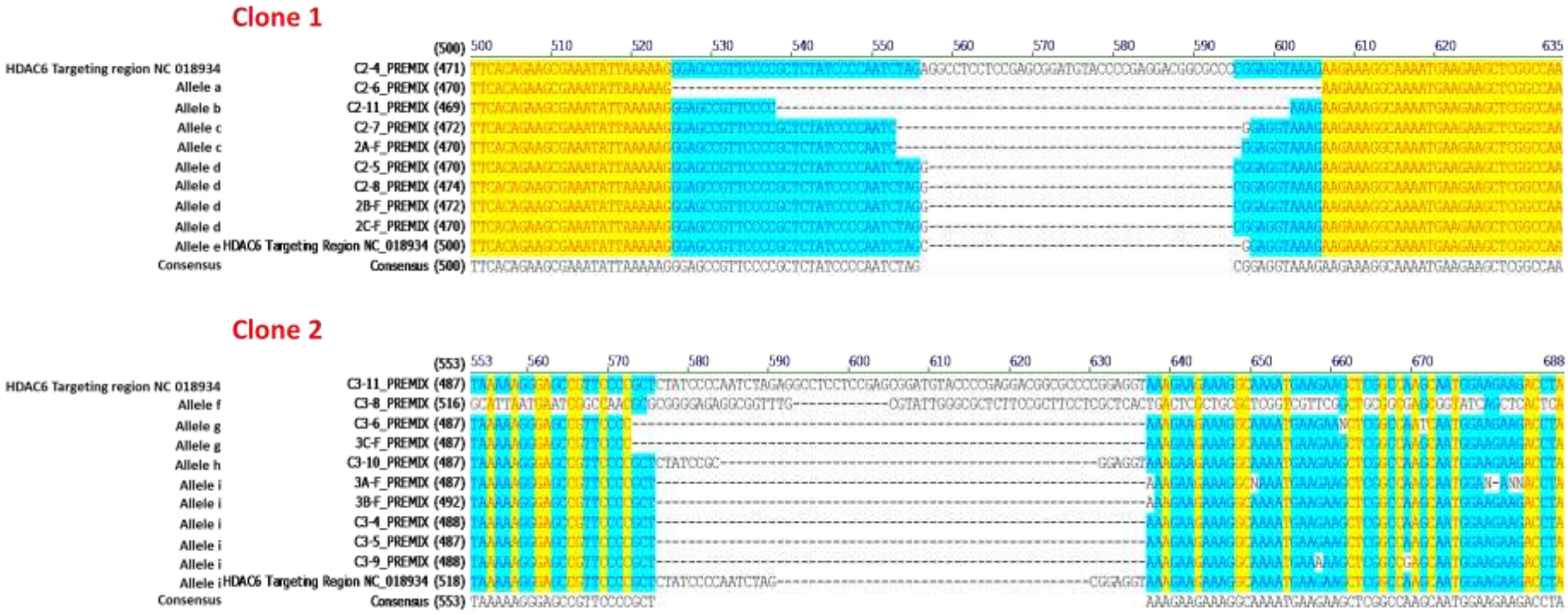
- How GeneCopoeia can help you with genome editing

Applications for genome editing

Application	Example	Technology	Reference
Gene knockout	Knockout SRY, UTY genes in cultured dells	TALEN via NHEJ and plasmid donor	Wang, et al. (2013). Nature Biotech. 31, 530
Gene knockout	Knockout of tet genes in transgenic rats	CRISPR via NHEJ	Li, et al. (2013). Nature Biotech. 8, 684
Correction of disease mutations	Cured heritable cataracts in transgenic mice	CRISPR via oligonucleotide donor	Wu, et al. (2013). Cell Stem Cell 13, 659
Engineered disease resistance	Knockout CCR5 gene to cure patients of HIV	ZFN via NHEJ	Perez, et al. (2008). Nat Biotech 26, 808
Forward mutagenesis screens	Identified genes in mismatch repair pathway by selecting for 6-thioguanosine resistance	CRISPR via NHEJ	Wang, et al. (2014). Science 343, 80
In-frame fusion tagging	C-terminal tag Sox2p with V5	CRISPR via oligonucleotide donor	Yang, et al. (2013). Cell 154, 1370
Transgene knock-in	Sox2, Oct4 ORFs KI into human AAVS1 “Safe Harbor”	TALEN via plasmid donor	GeneCopoeia internal data

Applications for genome editing

Knockout *via* NHEJ



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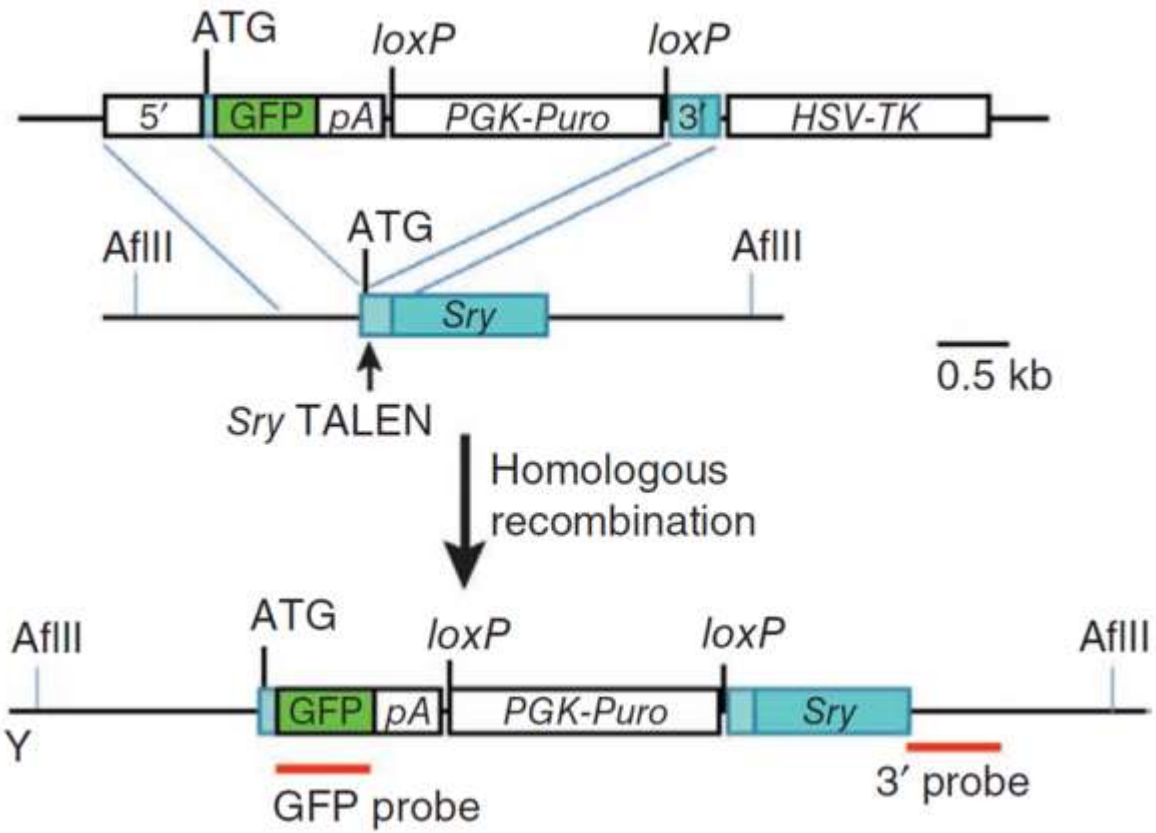
Applications for genome editing

Knockout *via* HDR: Donor plasmid



Wang, et al. (2013). Nature Biotech. 31, 530

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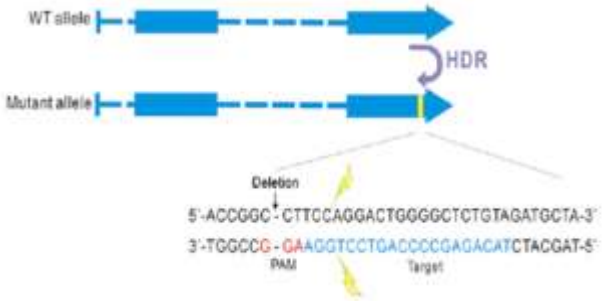
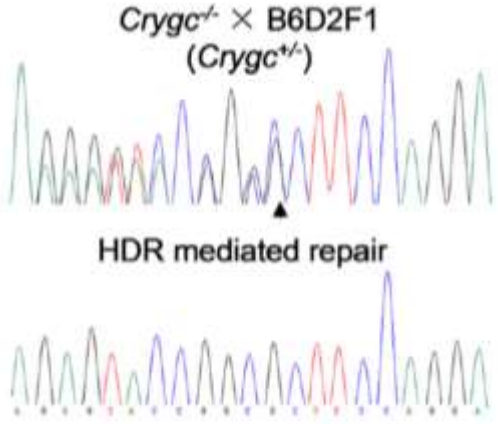
Applications for genome editing

Mutagenesis *via* HDR: Oligo donor





- Use single strand oligonucleotide (ssODN) to introduce base changes or small deletions.
- Use for mutagenesis or disease correction.
- Wu, et al.: Used CRISPR + ssODN to cure heritable cataract disease in mice

Wu, et al. (2013). Cell Stem Cell 13, 659

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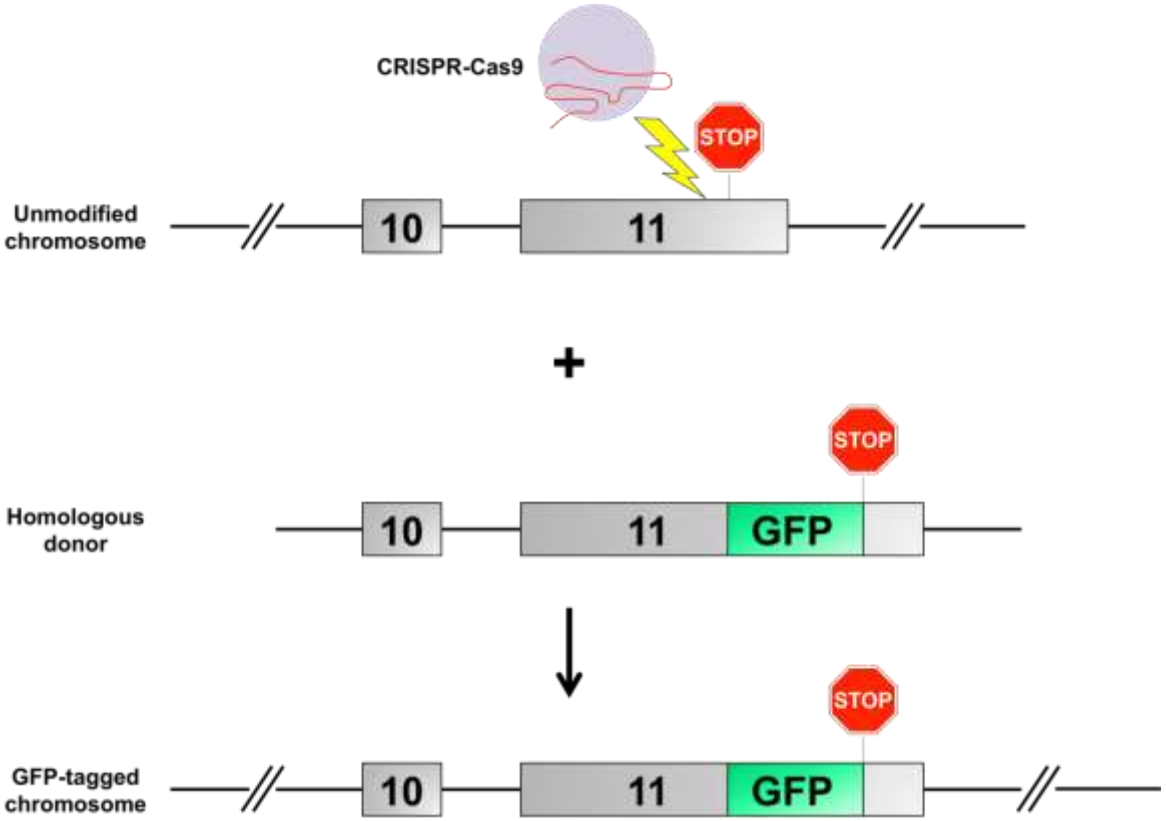
Applications for genome editing

In-frame fusion tagging



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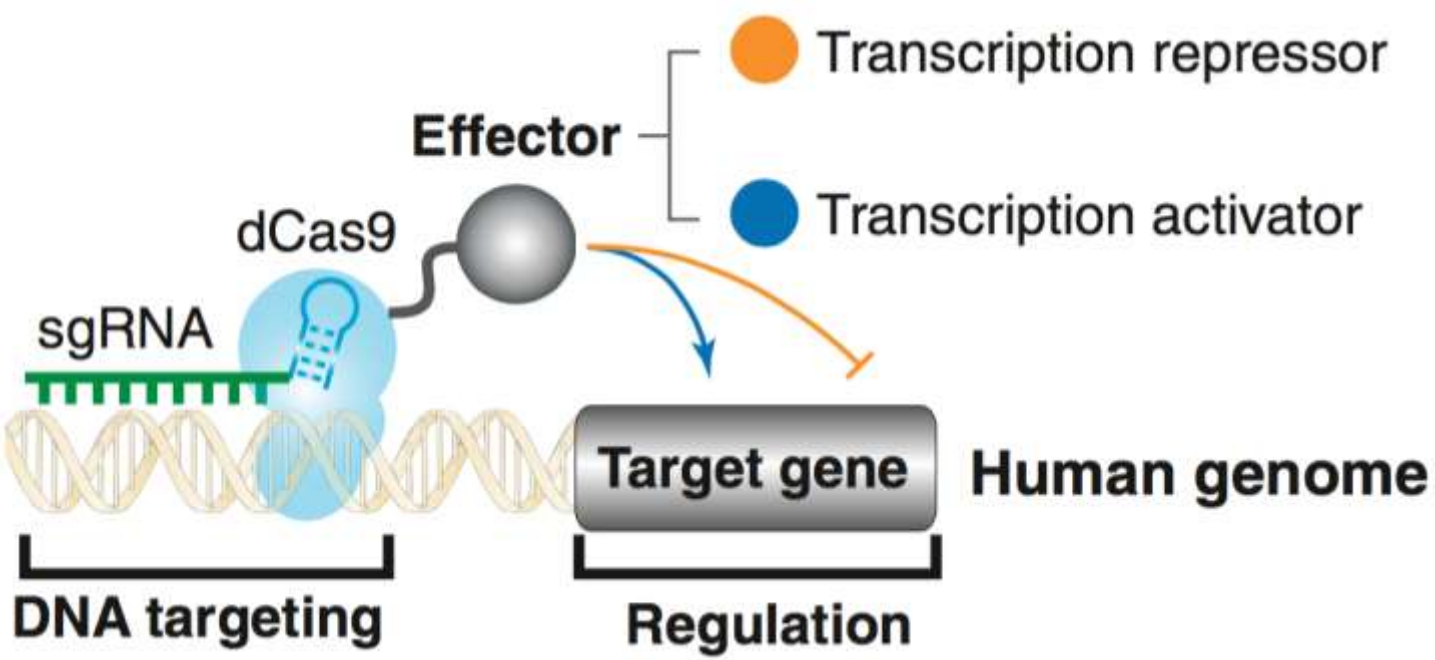
Applications for genome editing

Targeted gene activation/repression



Gilbert, et al. (2013). Cell 154, 442

Outline

- Genome editing: Technologies
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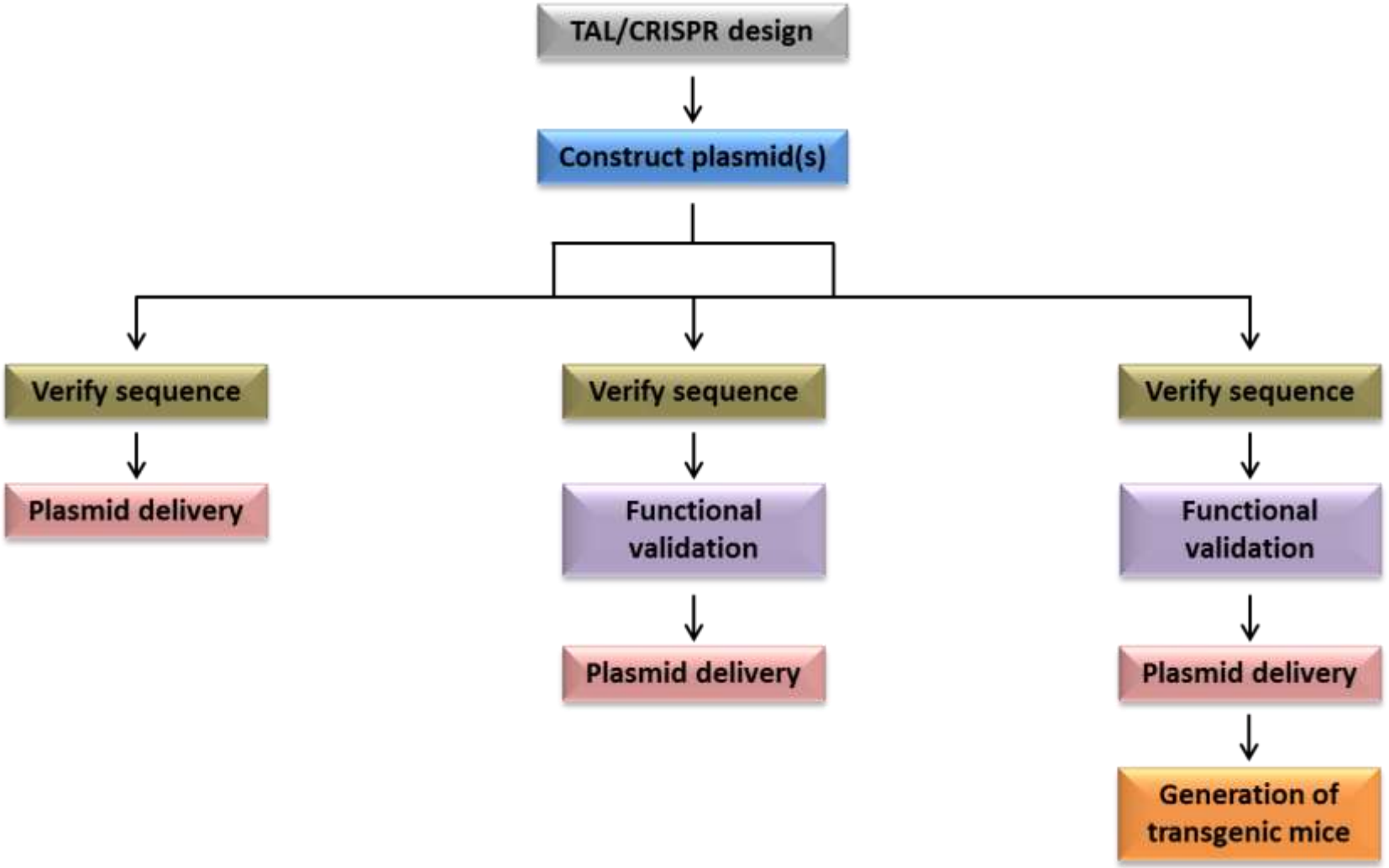
GeneCopoeia genome editing services



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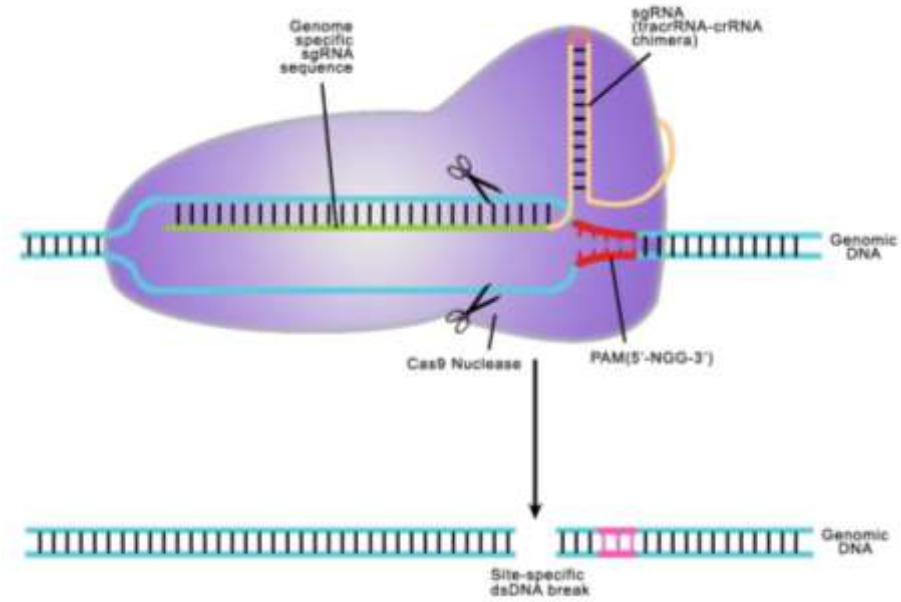
Custom CRISPR design & construction



Features

- Have nuclease (Cas9), activation (CRISPR-a) and repression (CRISPRi) systems
- Expert target design
- Plasmid construction process of the highest quality
- Quick turnaround time
- Advanced-level technical support

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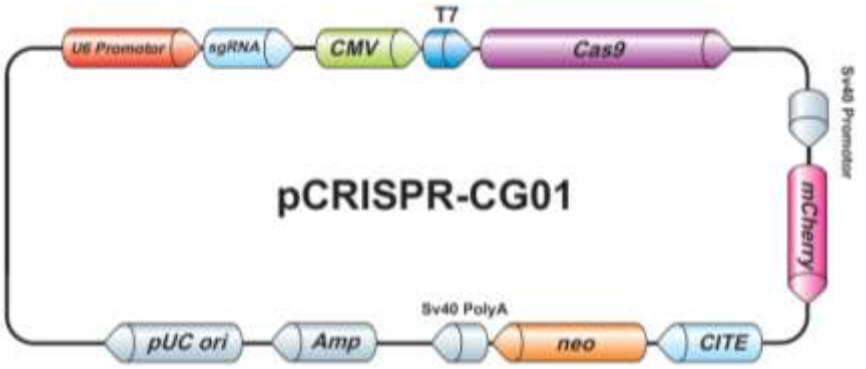
sgRNA plasmid design & construction

- Cas9 + sgRNA “All-in-one” plasmid



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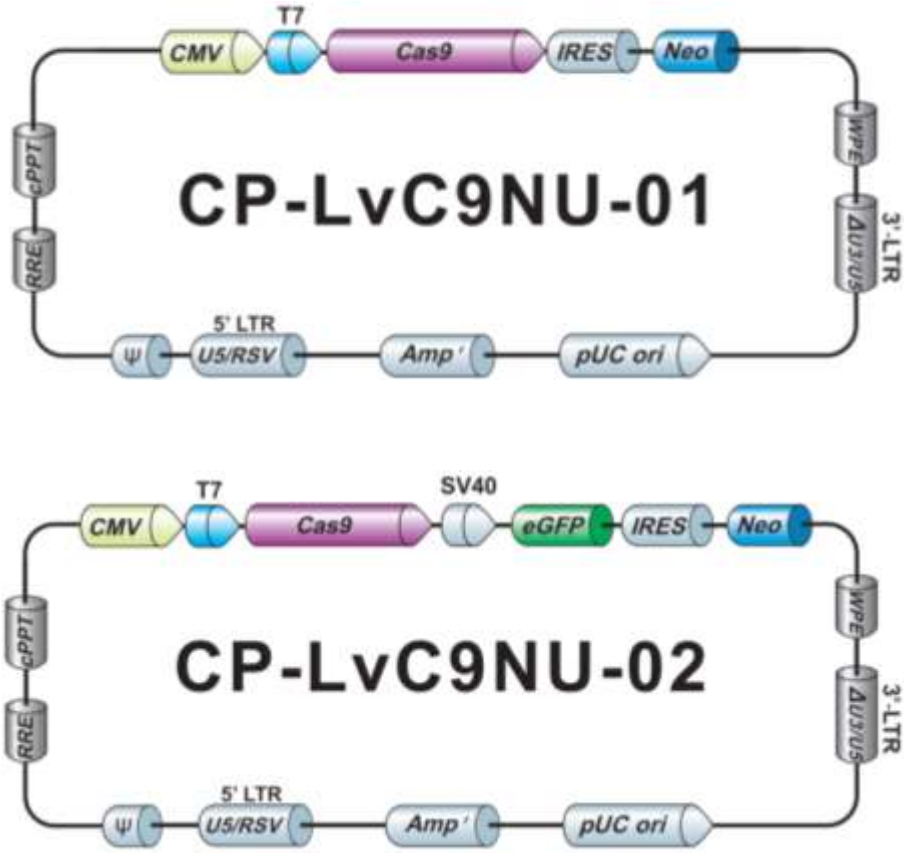
”Dual-use” lentiviral clones



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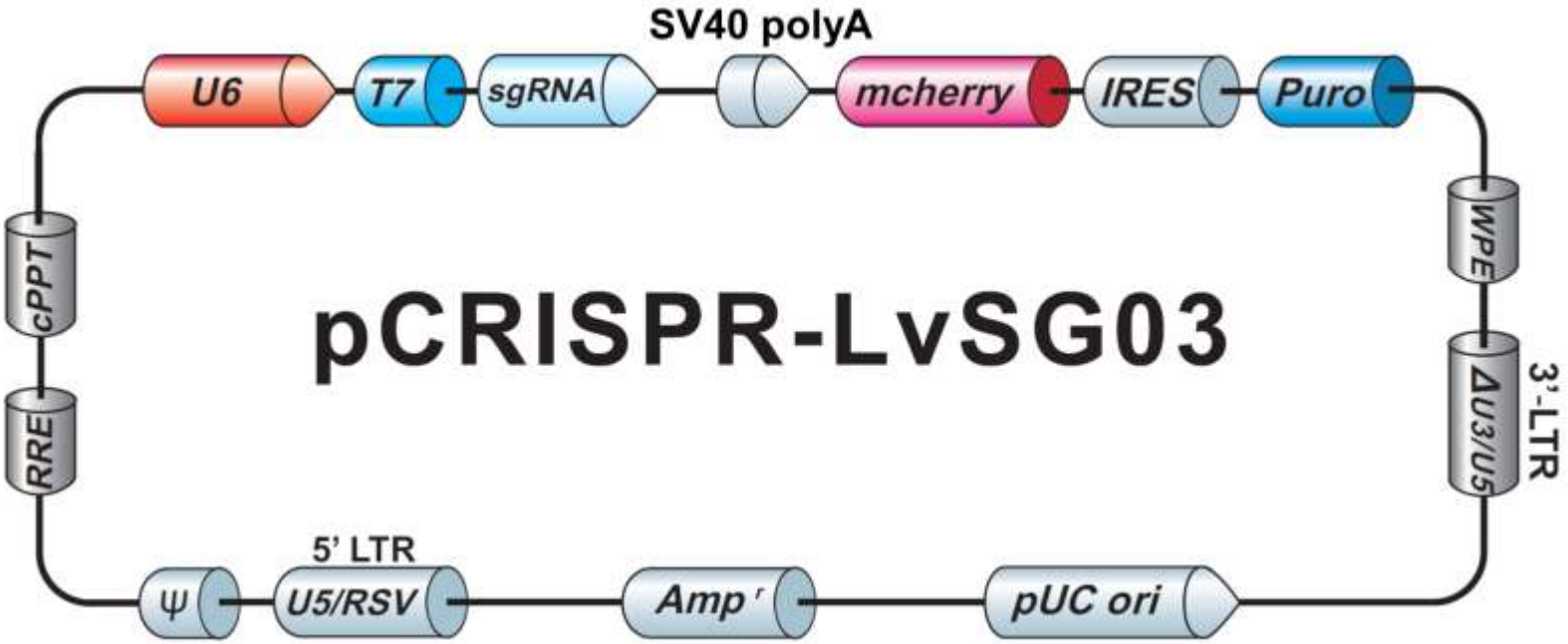
”Dual-use” lentiviral clones



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GeneCopoeia sgRNA libraries

Pathway & gene group sgRNA libraries

Library name	Number of genes
Innate kinases & ubiquitin ligases	239
Nuclear hormone receptors	118
Tumor metastasis genes	57
Oncogenes	288
Tumor suppressor genes	231
Protein kinases	658
Key genes in 50 pathways	139
Custom	Made-to-order

Available as bacteria, DNA, or lentiviral particles either:

A. **Pooled**

B. **Individually arrayed**

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GeneCopoeia sgRNA libraries

Advantages

- Individually constructed and cultured in *E. coli* before pooling. Makes possible use in pools or as individual sgRNAs.
- Pools limited to 150 sgRNAs, ensuring excellent representation of each sgRNA
- Sequence verification provides high quality of each sgRNA
- Small library sizes: Reduces time and cost of screening

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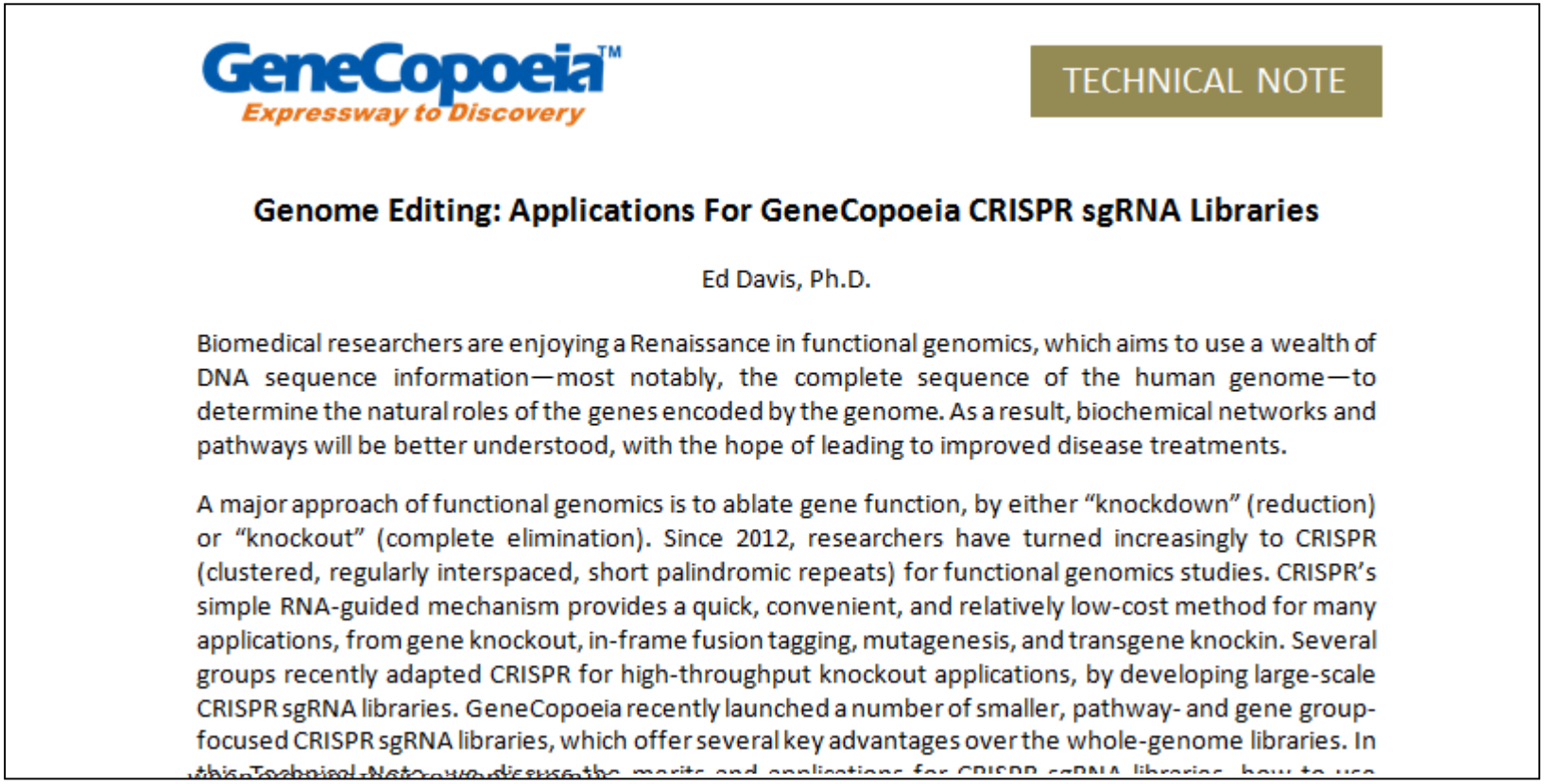
GeneCopoeia sgRNA libraries

GeneCopoeia Technical Note: sgRNA libraries



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TECHNICAL NOTE

Genome Editing: Applications For GeneCopoeia CRISPR sgRNA Libraries

Ed Davis, Ph.D.

Biomedical researchers are enjoying a Renaissance in functional genomics, which aims to use a wealth of DNA sequence information—most notably, the complete sequence of the human genome—to determine the natural roles of the genes encoded by the genome. As a result, biochemical networks and pathways will be better understood, with the hope of leading to improved disease treatments.

A major approach of functional genomics is to ablate gene function, by either "knockdown" (reduction) or "knockout" (complete elimination). Since 2012, researchers have turned increasingly to CRISPR (clustered, regularly interspaced, short palindromic repeats) for functional genomics studies. CRISPR's simple RNA-guided mechanism provides a quick, convenient, and relatively low-cost method for many applications, from gene knockout, in-frame fusion tagging, mutagenesis, and transgene knockin. Several groups recently adapted CRISPR for high-throughput knockout applications, by developing large-scale CRISPR sgRNA libraries. GeneCopoeia recently launched a number of smaller, pathway- and gene group-focused CRISPR sgRNA libraries, which offer several key advantages over the whole-genome libraries. In this Technical Note, we discuss the merits and applications for CRISPR sgRNA libraries, how to use

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Donor plasmid design services

Why use a donor?

- Donor plasmids needed for HR-mediated transgene knockin
- Knocked in selectable & fluorescent markers can be identified easily. NHEJ mutations have no selection. Good for low transfection efficiency
- HR-mediated mutations are predicable, unlike NHEJ-mediated mutations

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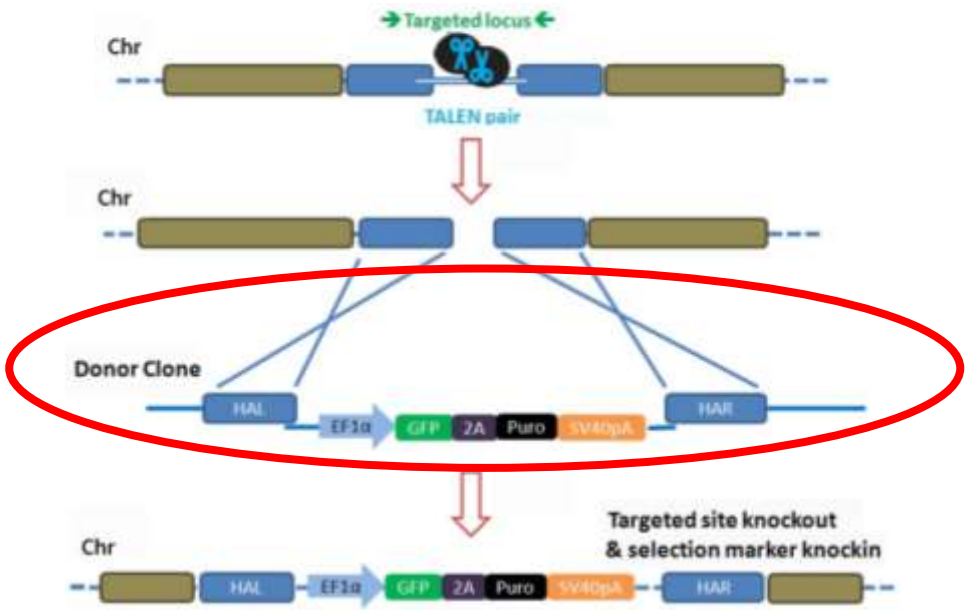
Donor plasmid design services



Features

- Homologous arms flanking targeted site are engineered to flank markers for drug selection, fluorescence, and more
- Markers flanked by loxP sites for Cre-mediated removal, if desired

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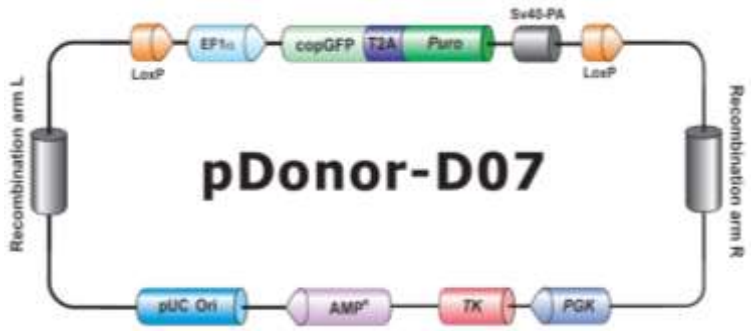
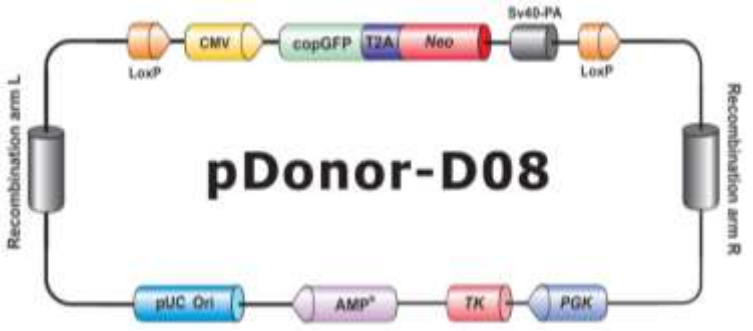
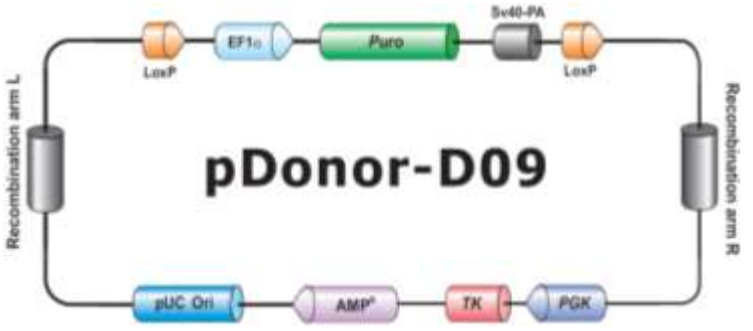
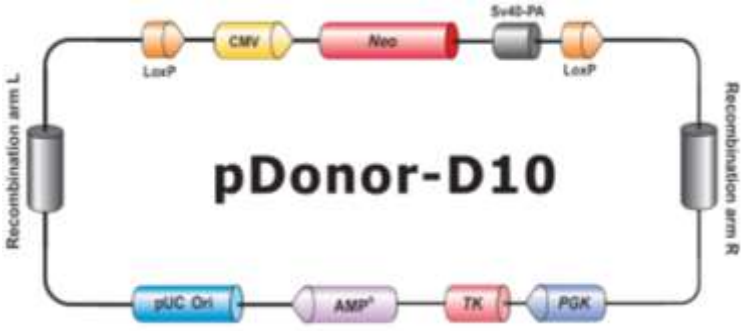
Donor plasmid design services & DIY cloning vectors









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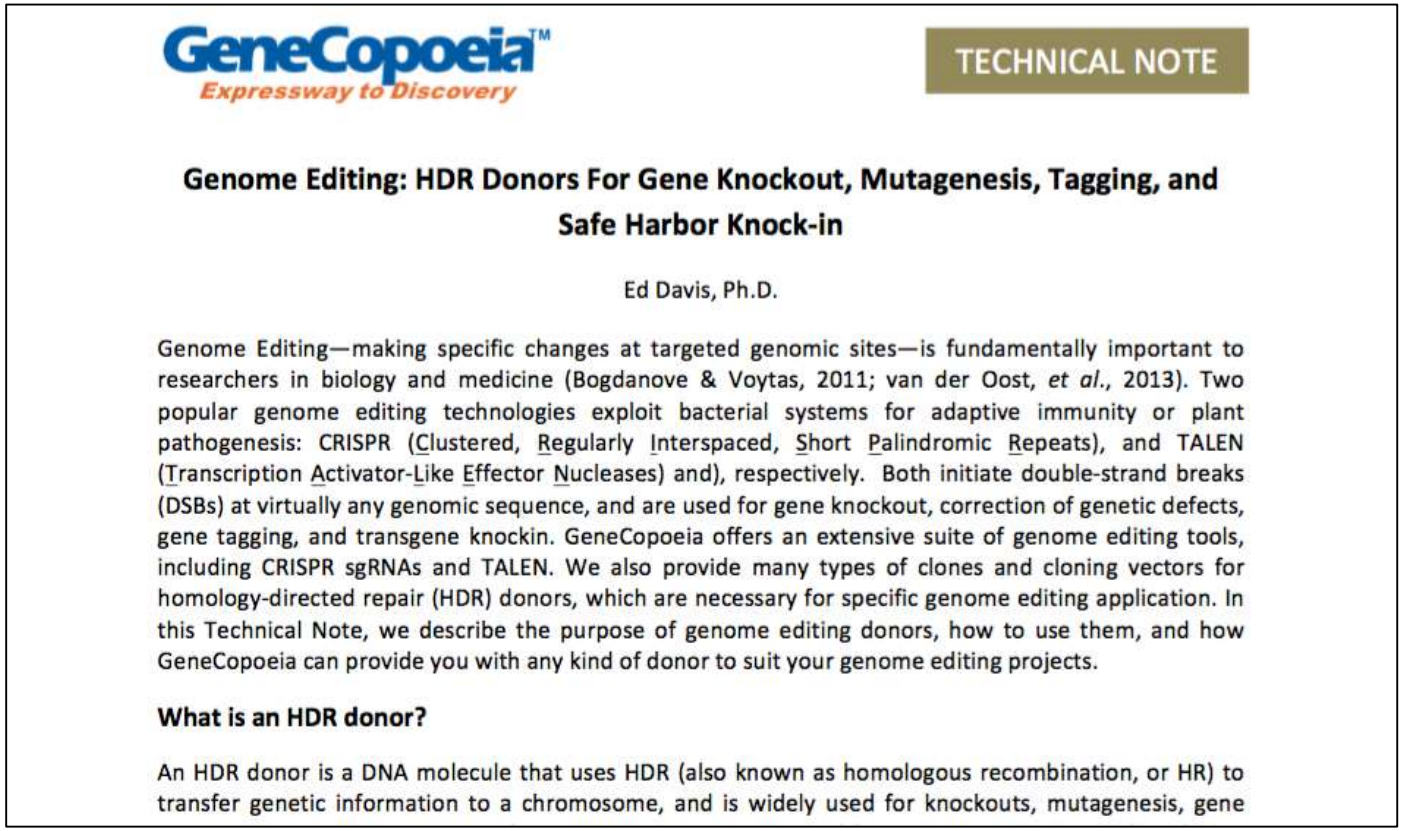
GeneCopoeia Technical Note: Donor clones



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TECHNICAL NOTE

Genome Editing: HDR Donors For Gene Knockout, Mutagenesis, Tagging, and Safe Harbor Knock-in

Ed Davis, Ph.D.

Genome Editing—making specific changes at targeted genomic sites—is fundamentally important to researchers in biology and medicine (Bogdanove & Voytas, 2011; van der Oost, *et al.*, 2013). Two popular genome editing technologies exploit bacterial systems for adaptive immunity or plant pathogenesis: CRISPR (Clustered, Regularly Interspaced, Short Palindromic Repeats), and TALEN (Transcription Activator-Like Effector Nucleases) and), respectively. Both initiate double-strand breaks (DSBs) at virtually any genomic sequence, and are used for gene knockout, correction of genetic defects, gene tagging, and transgene knockin. GeneCopoeia offers an extensive suite of genome editing tools, including CRISPR sgRNAs and TALEN. We also provide many types of clones and cloning vectors for homology-directed repair (HDR) donors, which are necessary for specific genome editing application. In this Technical Note, we describe the purpose of genome editing donors, how to use them, and how GeneCopoeia can provide you with any kind of donor to suit your genome editing projects.

What is an HDR donor?

An HDR donor is a DNA molecule that uses HDR (also known as homologous recombination, or HR) to transfer genetic information to a chromosome, and is widely used for knockouts, mutagenesis, gene

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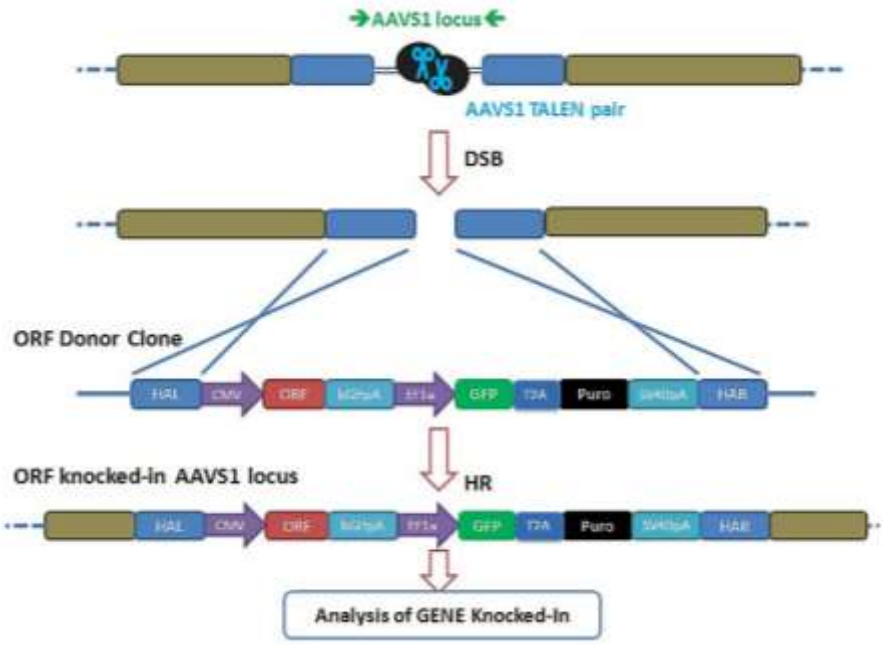
Safe Harbor



Features

- Human AAVS1 & mouse Rosa26 sites ensure transcription-competency of the transgenes & present no known adverse effects on cells
- Safe Harbor integration provides low copy number of transgene & close to physiological-level expression.

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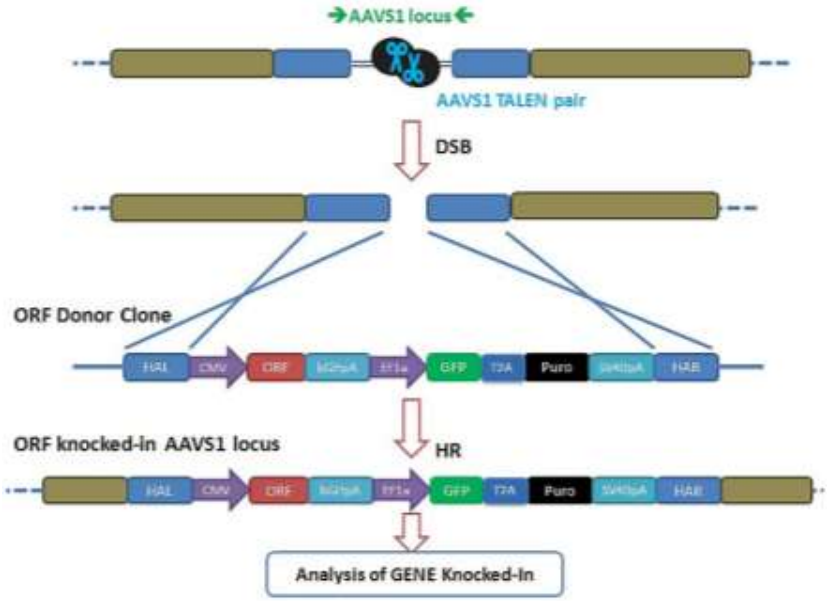
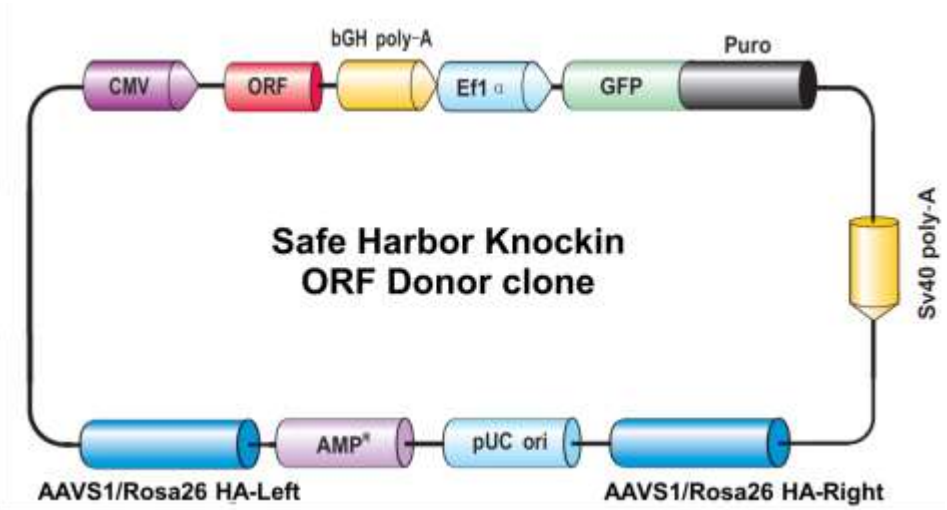
Safe Harbor knock-in ORF clones





Features

- Over 40,000 sequence-verified human & mouse ORFs available
- Inserted between AAVS1 or Rosa26 sites for ready safe harbor integration

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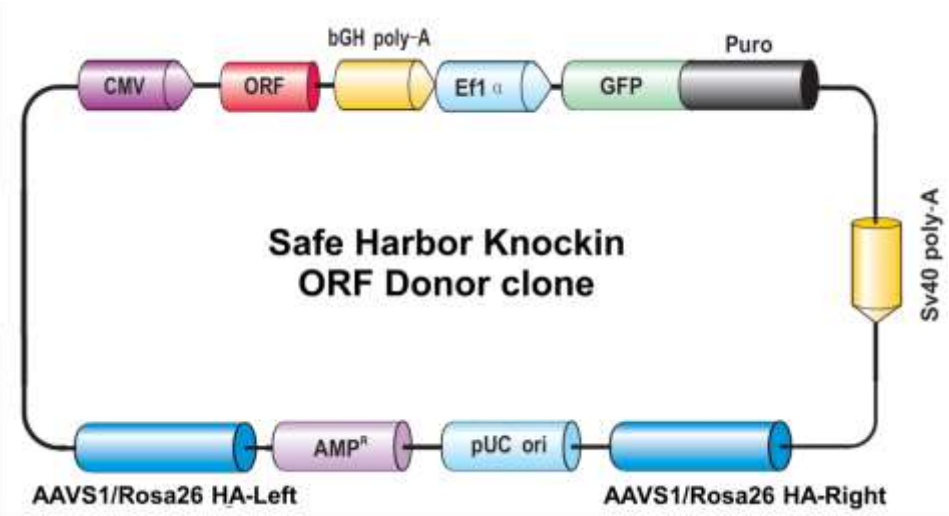
Safe Harbor knock-in ORF clones



Some applications for Safe Harbor knockin ORF clones:

- Rescue of a knockout or mutagenesis phenotype
- Overexpression of a fusion tagged protein
- Expression of a gene from a different species (e.g. human gene in a mouse)

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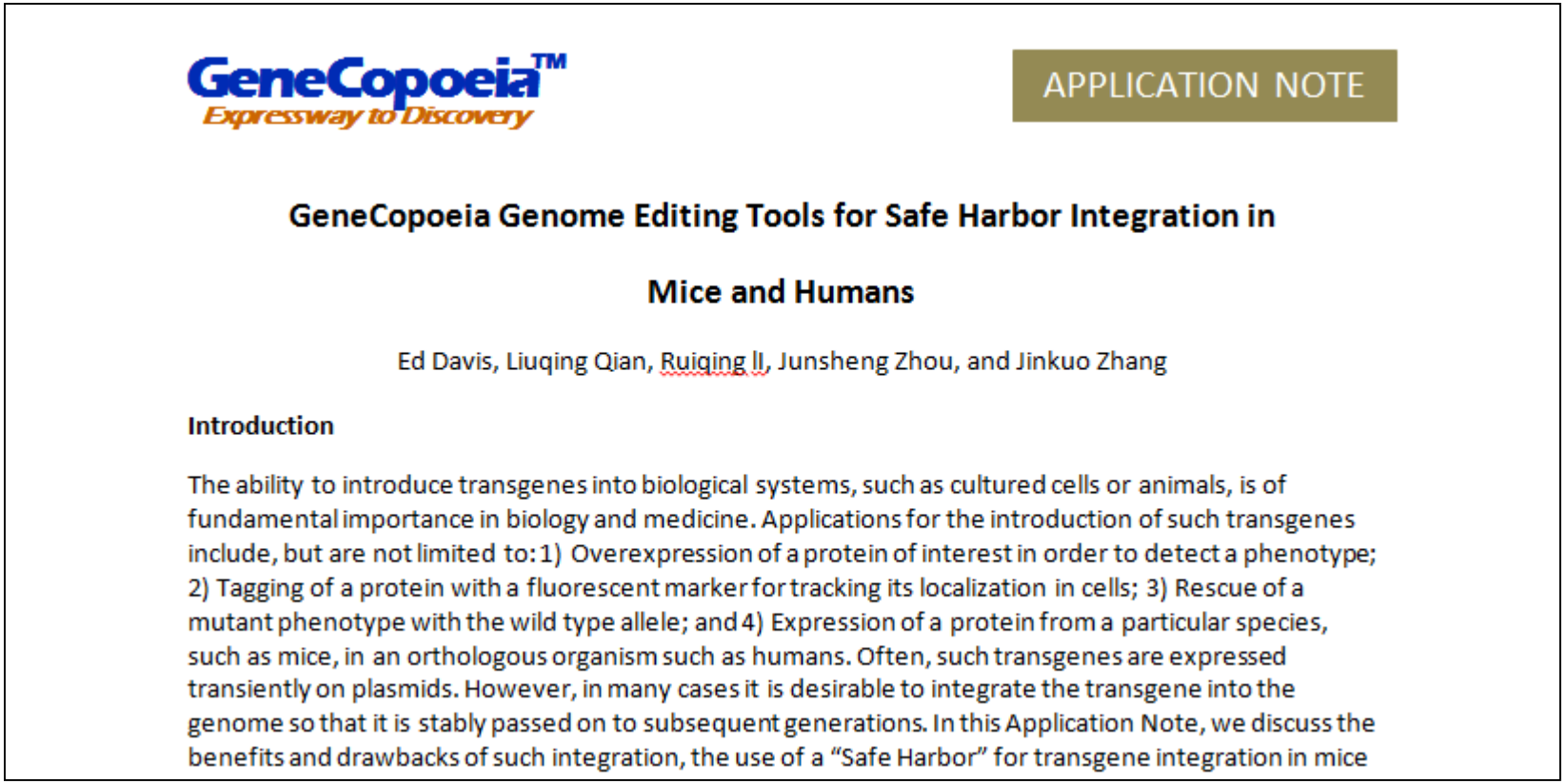
GeneCopoeia Application Note: Safe Harbor



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APPLICATION NOTE

GeneCopoeia Genome Editing Tools for Safe Harbor Integration in Mice and Humans

Ed Davis, Liuqing Qian, Ruiqing li, Junsheng Zhou, and Jinkuo Zhang

Introduction

The ability to introduce transgenes into biological systems, such as cultured cells or animals, is of fundamental importance in biology and medicine. Applications for the introduction of such transgenes include, but are not limited to: 1) Overexpression of a protein of interest in order to detect a phenotype; 2) Tagging of a protein with a fluorescent marker for tracking its localization in cells; 3) Rescue of a mutant phenotype with the wild type allele; and 4) Expression of a protein from a particular species, such as mice, in an orthologous organism such as humans. Often, such transgenes are expressed transiently on plasmids. However, in many cases it is desirable to integrate the transgene into the genome so that it is stably passed on to subsequent generations. In this Application Note, we discuss the benefits and drawbacks of such integration, the use of a "Safe Harbor" for transgene integration in mice

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http://www.genecopoeia.com/wp-content/uploads/2014/04/Application_note_Safe_Harbor.pdf

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GeneCopoeia genome editing services

What do I do next?

- Downstream work: Following transfection
- NHEJ-mediated applications: Might need to screen many colonies to detect modifications
- HR-mediated applications: Need to rule out random integration of donor plasmid
- All applications: Might need to mutagenize again or screen more clones for double allele modification

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Functional validation

Why do functional validation?

- Cell culture-based genome editing projects can take 3 or more months to complete
- Not all CRISPR sgRNAs are created equal! Test first before undergoing long genome editing project to avoid wasting time and expense.
- Recommend cell culture based strategy using T7 Endonuclease I assay.

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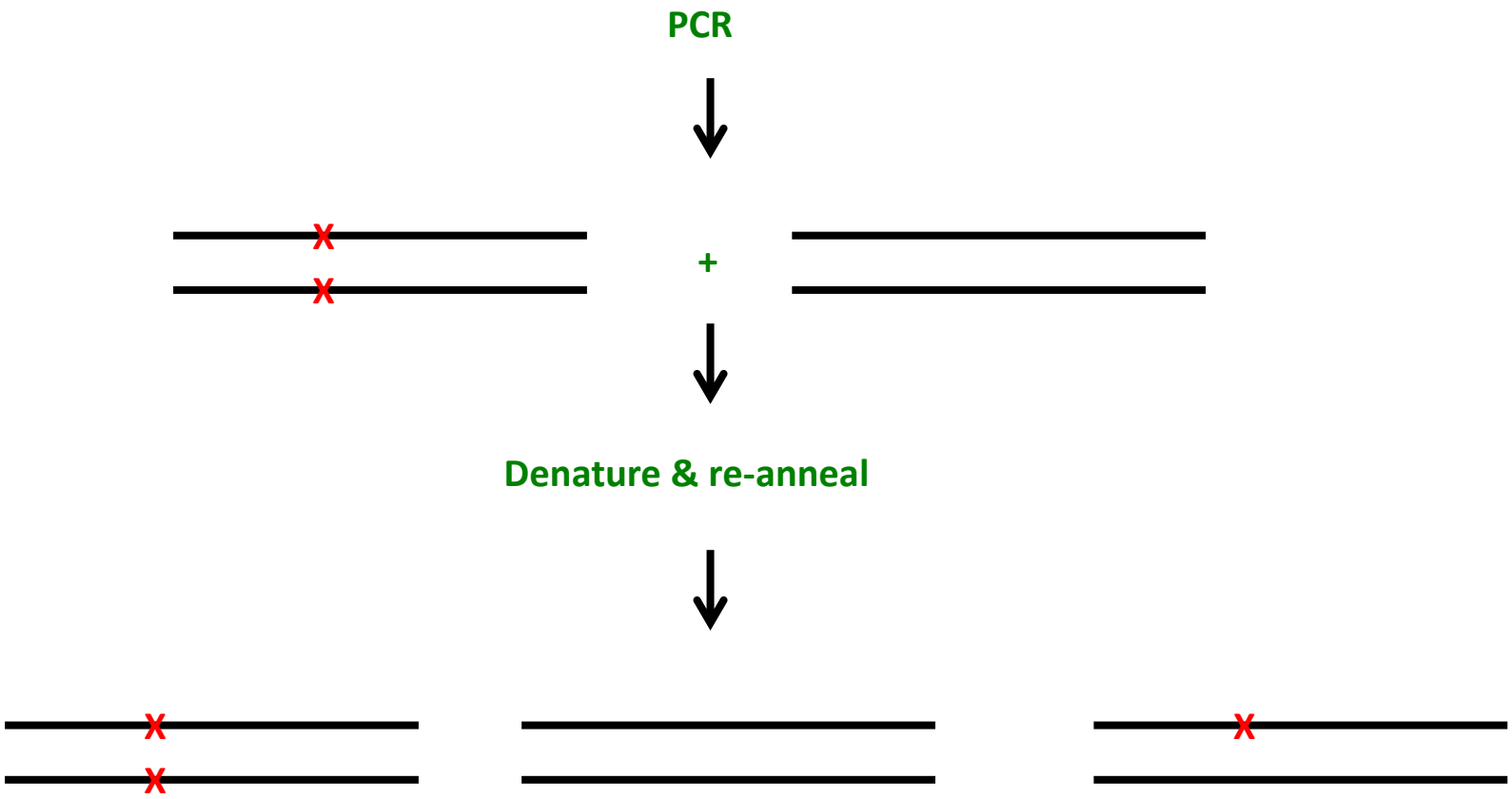
Functional validation



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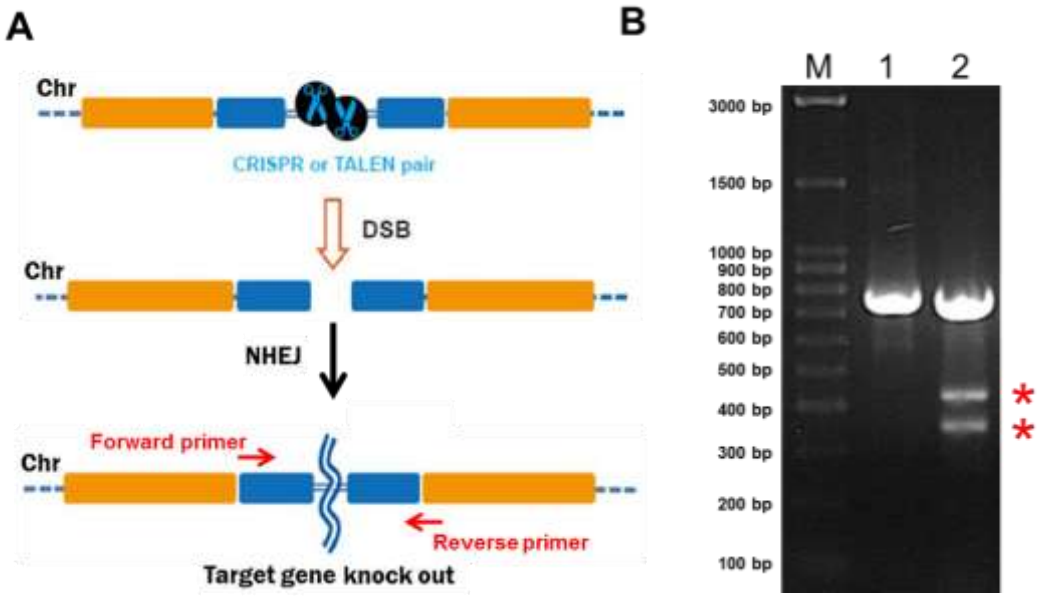
Functional validation

IndelCheck™ T7 Endonuclease System



- Contains PCR and T7 endonuclease I reagents
- Purchase with or without target-specific primers

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Functional validation

GeneCopoeia functional validation services

- Additional service available for human and mouse sgRNAs
- GeneCopoeia will transfect human (HEK293) or mouse (Neuro2A) cells with custom sgRNA plasmids
- GeneCopoeia will isolate DNA from bulk population of cells and perform T7 Endonuclease I assay
- Customer is provided with validation report

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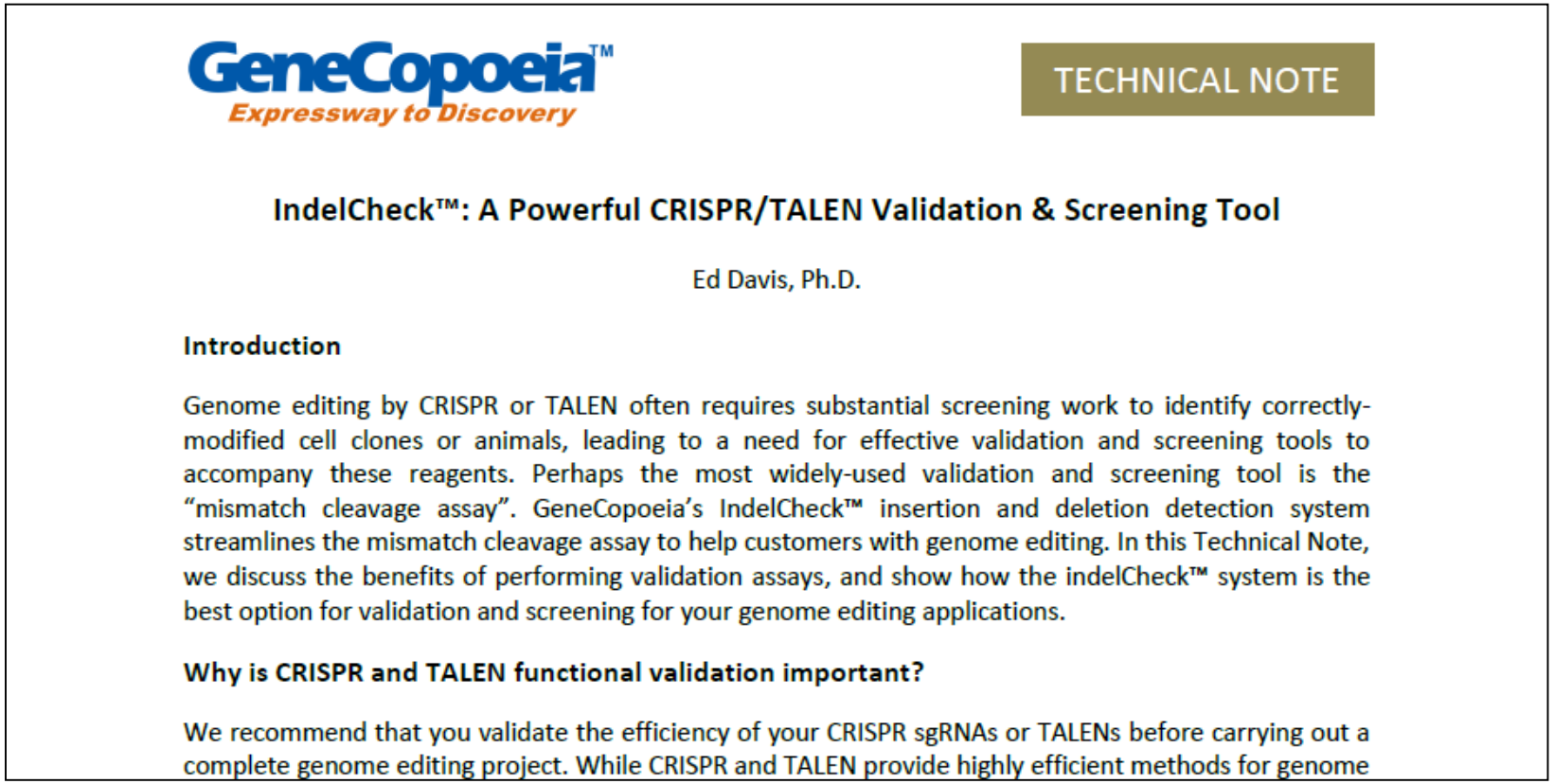
Functional validation

GeneCopoeia Technical Note: IndelCheck™ kit



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TECHNICAL NOTE

IndelCheck™: A Powerful CRISPR/TALEN Validation & Screening Tool

Ed Davis, Ph.D.

Introduction

Genome editing by CRISPR or TALEN often requires substantial screening work to identify correctly-modified cell clones or animals, leading to a need for effective validation and screening tools to accompany these reagents. Perhaps the most widely-used validation and screening tool is the "mismatch cleavage assay". GeneCopoeia's IndelCheck™ insertion and deletion detection system streamlines the mismatch cleavage assay to help customers with genome editing. In this Technical Note, we discuss the benefits of performing validation assays, and show how the indelCheck™ system is the best option for validation and screening for your genome editing applications.

Why is CRISPR and TALEN functional validation important?

We recommend that you validate the efficiency of your CRISPR sgRNAs or TALENs before carrying out a complete genome editing project. While CRISPR and TALEN provide highly efficient methods for genome

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http://www.genecopoeia.com/wp-content/uploads/2015/07/GeneCopoeia-Technical-Note-IndelCheck-system-07-2015.pdf

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Copy number determination

Why do copy number determination?

- For complete knockouts or mutagenesis, might need to modify all alleles
- Not all cell lines are diploid. Some lines, like HeLa, have 3, 4, or more genomes!
- Would expect multi-allele modification to be more difficult to achieve than single allele
- However, one publication showed that double allele occurs more frequently than single allele (Gonzalez, et al., 2014. Cell Stem Cell 15, 1)

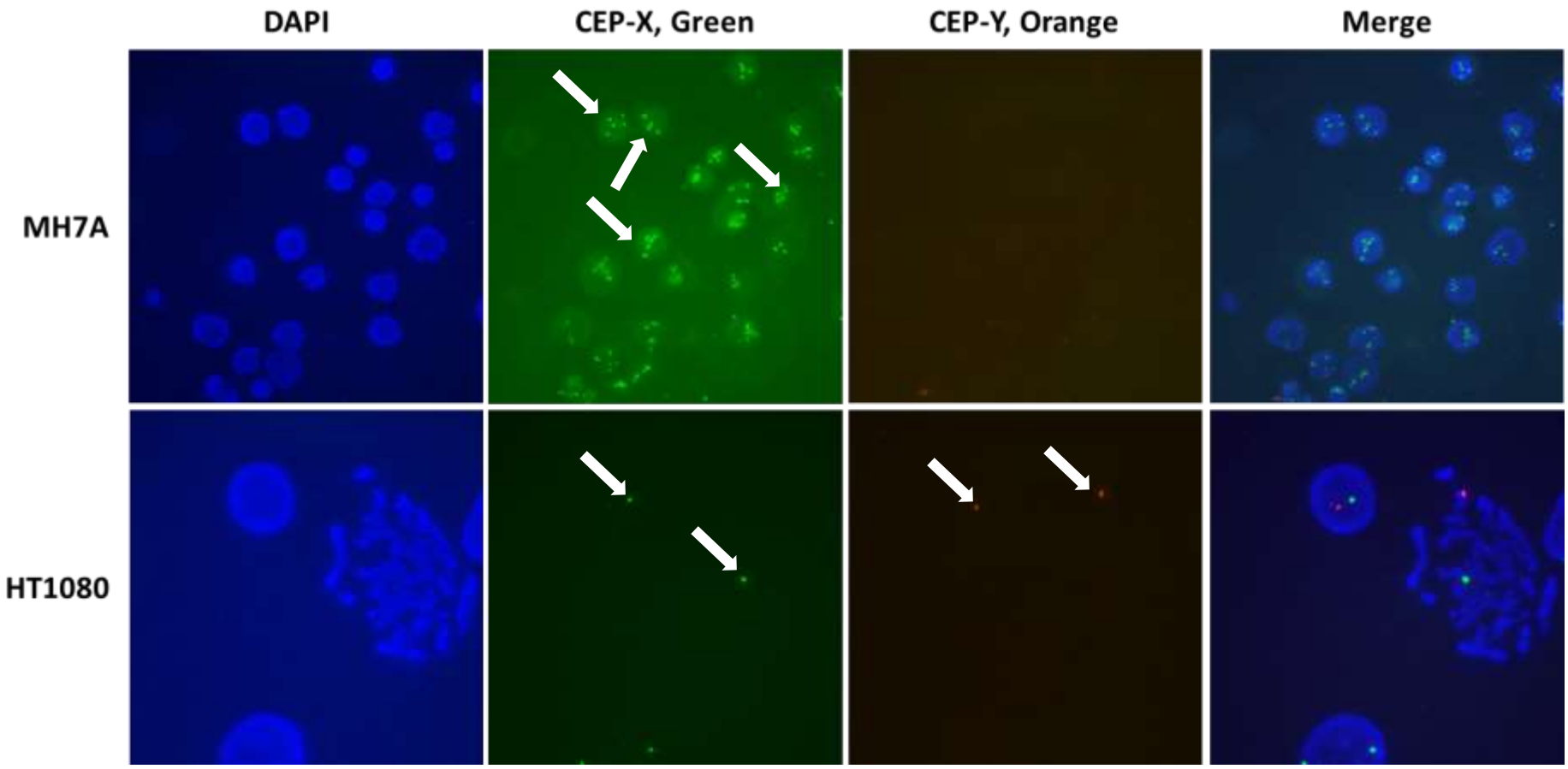
Copy number determination

Application: Using FISH with a CRISPR knockout

- Project: Knock out HDAC6 gene in human MH7A cells
- HDAC6 (NCBI geneID:10013): Located on X chromosome (Xp11.23)
- MH7A cells: Human immortalized synovial fibroblast line
- HDAC6 copy number: Unknown

Copy number determination

Application: Using FISH with a CRISPR knockout



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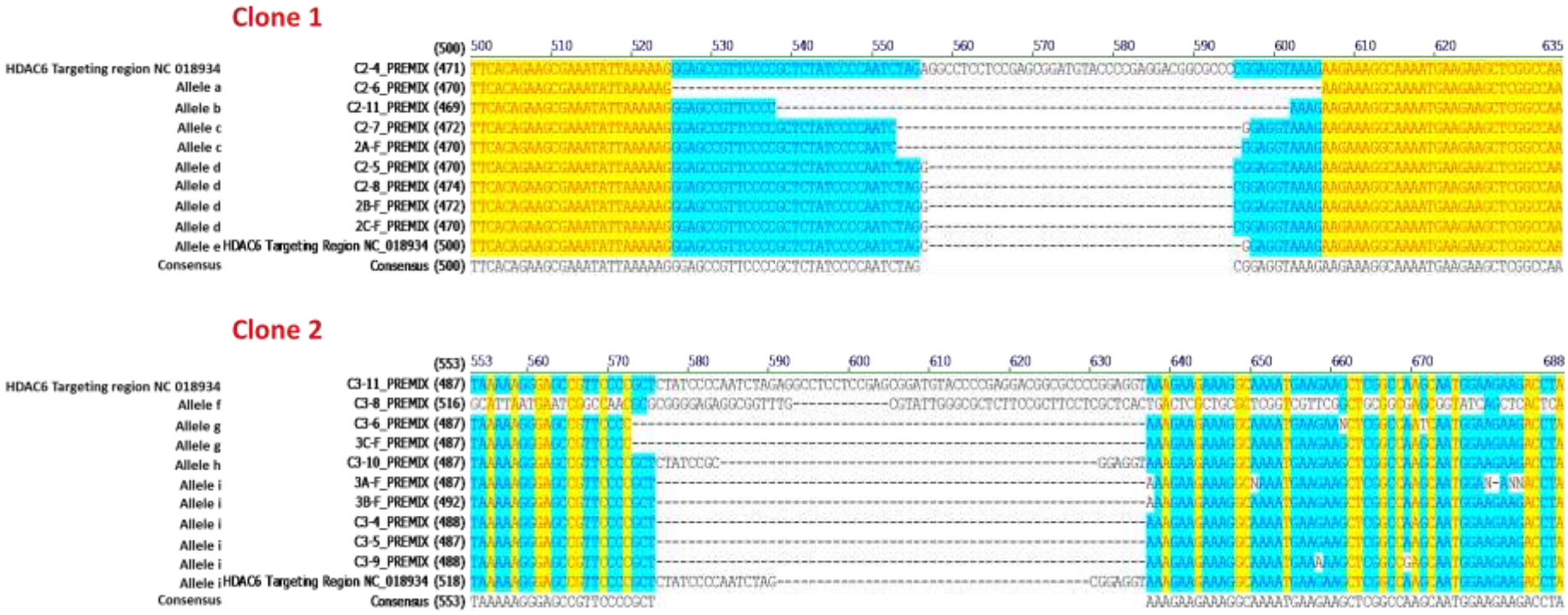
Copy number determination

Application: Using FISH with a CRISPR knockout



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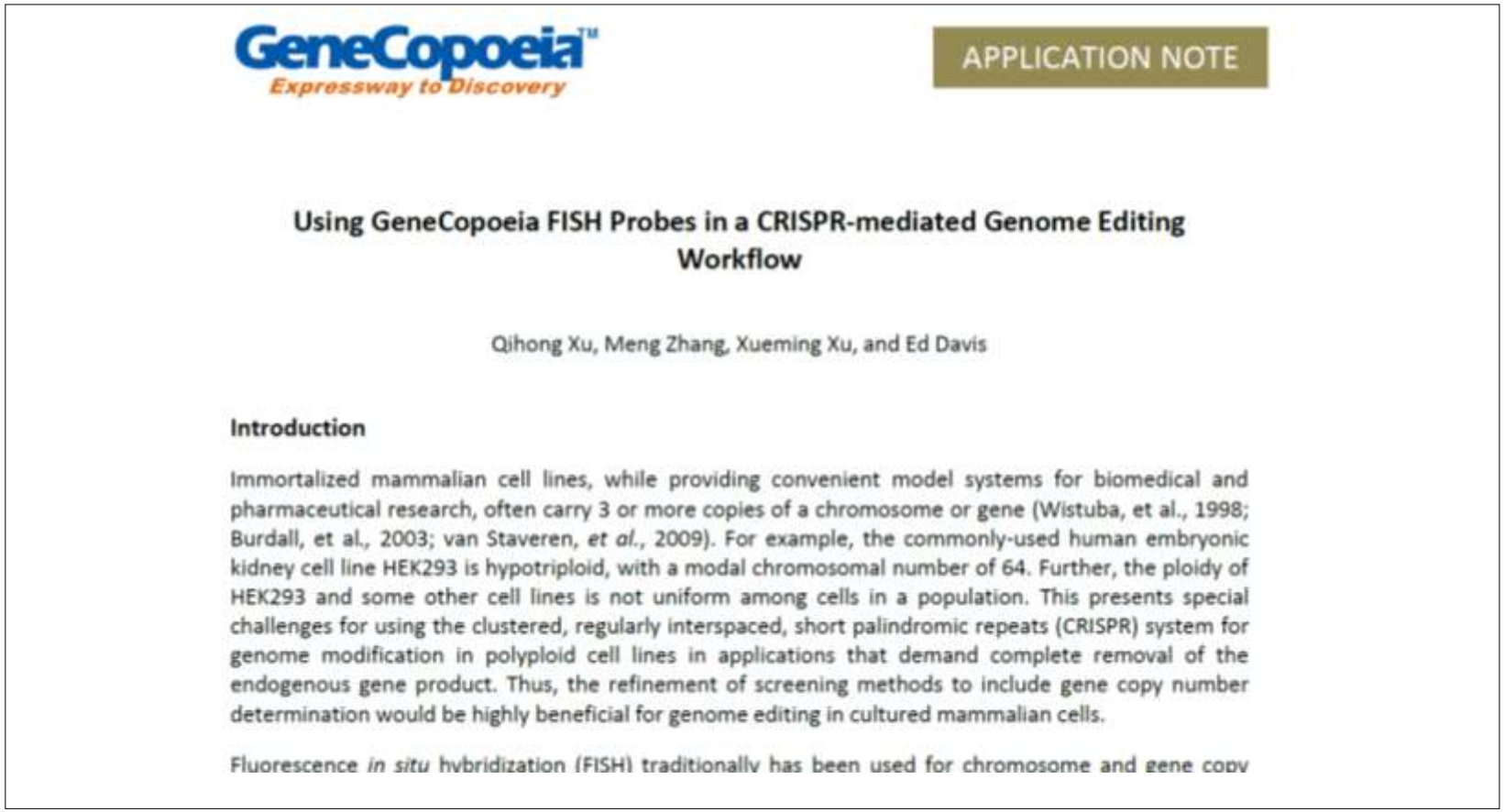
Copy number determination

GeneCopoeia Application Note: FISH with CRISPR



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APPLICATION NOTE

Using GeneCopoeia FISH Probes in a CRISPR-mediated Genome Editing Workflow

Qihong Xu, Meng Zhang, Xueming Xu, and Ed Davis

Introduction

Immortalized mammalian cell lines, while providing convenient model systems for biomedical and pharmaceutical research, often carry 3 or more copies of a chromosome or gene (Wistuba, et al., 1998; Burdall, et al., 2003; van Staveren, *et al.*, 2009). For example, the commonly-used human embryonic kidney cell line HEK293 is hypotriploid, with a modal chromosomal number of 64. Further, the ploidy of HEK293 and some other cell lines is not uniform among cells in a population. This presents special challenges for using the clustered, regularly interspaced, short palindromic repeats (CRISPR) system for genome modification in polyploid cell lines in applications that demand complete removal of the endogenous gene product. Thus, the refinement of screening methods to include gene copy number determination would be highly beneficial for genome editing in cultured mammalian cells.

Fluorescence *in situ* hybridization (FISH) traditionally has been used for chromosome and gene copy

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http://www.genecopoeia.com/wp-content/uploads/2016/02/FISH-for-CRISPR.pdf

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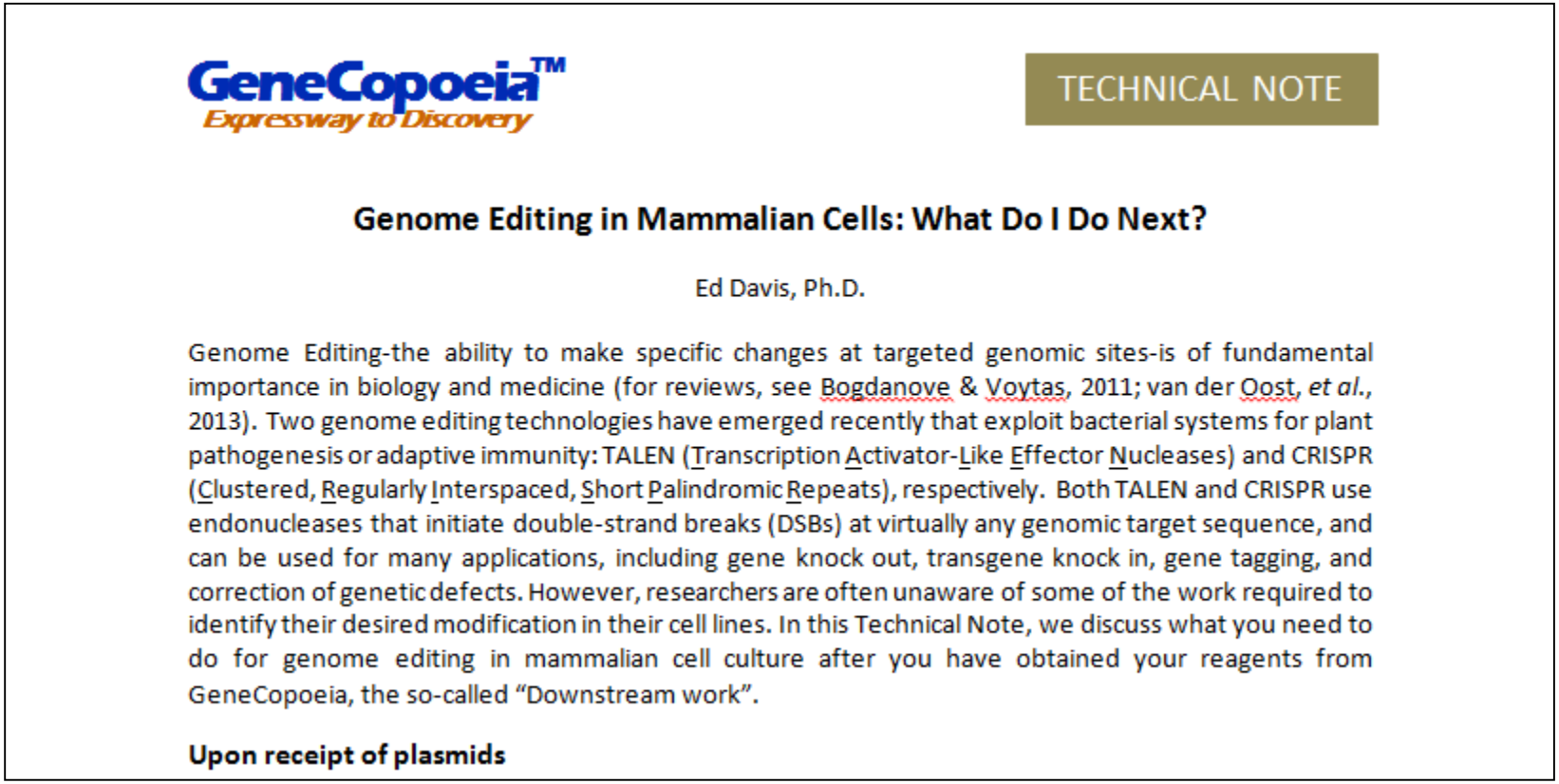
Copy number determination

GeneCopoeia Application Note: Downstream work



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TECHNICAL NOTE

Genome Editing in Mammalian Cells: What Do I Do Next?

Ed Davis, Ph.D.

Genome Editing-the ability to make specific changes at targeted genomic sites-is of fundamental importance in biology and medicine (for reviews, see Bogdanove & Voytas, 2011; van der Oost, *et al.*, 2013). Two genome editing technologies have emerged recently that exploit bacterial systems for plant pathogenesis or adaptive immunity: TALEN (Transcription Activator-Like Effector Nucleases) and CRISPR (Clustered, Regularly Interspaced, Short Palindromic Repeats), respectively. Both TALEN and CRISPR use endonucleases that initiate double-strand breaks (DSBs) at virtually any genomic target sequence, and can be used for many applications, including gene knock out, transgene knock in, gene tagging, and correction of genetic defects. However, researchers are often unaware of some of the work required to identify their desired modification in their cell lines. In this Technical Note, we discuss what you need to do for genome editing in mammalian cell culture after you have obtained your reagents from GeneCopoeia, the so-called "Downstream work".

Upon receipt of plasmids

Download from:

http://www.genecopoeia.com/wp-content/uploads/2015/07/Downstream-work-07.pdf

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GeneCopoeia genome editing services

Cas9-expressing stable cell lines

- Cell lines with stably expressing Cas9
- Have pre-made lines, or can have us integrate Cas9 in your cell line
- Donor clone available for DIY stable cell line creation
- Cas9 integrated at Safe harbor locus for high expression and insertion without consequences
- Ideal for sgRNA library screening or validation

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GeneCopoeia genome editing services

CRISPR transgenic mouse services

Features

- Design, construction, & functional validation of CRISPR sgRNAs
- Design & construction of homologous donors (if needed)
- Injection of Cas9 RNA, sgRNA, and donor DNA into zygotes
- Deliver at least 3 F1 heterozygotes

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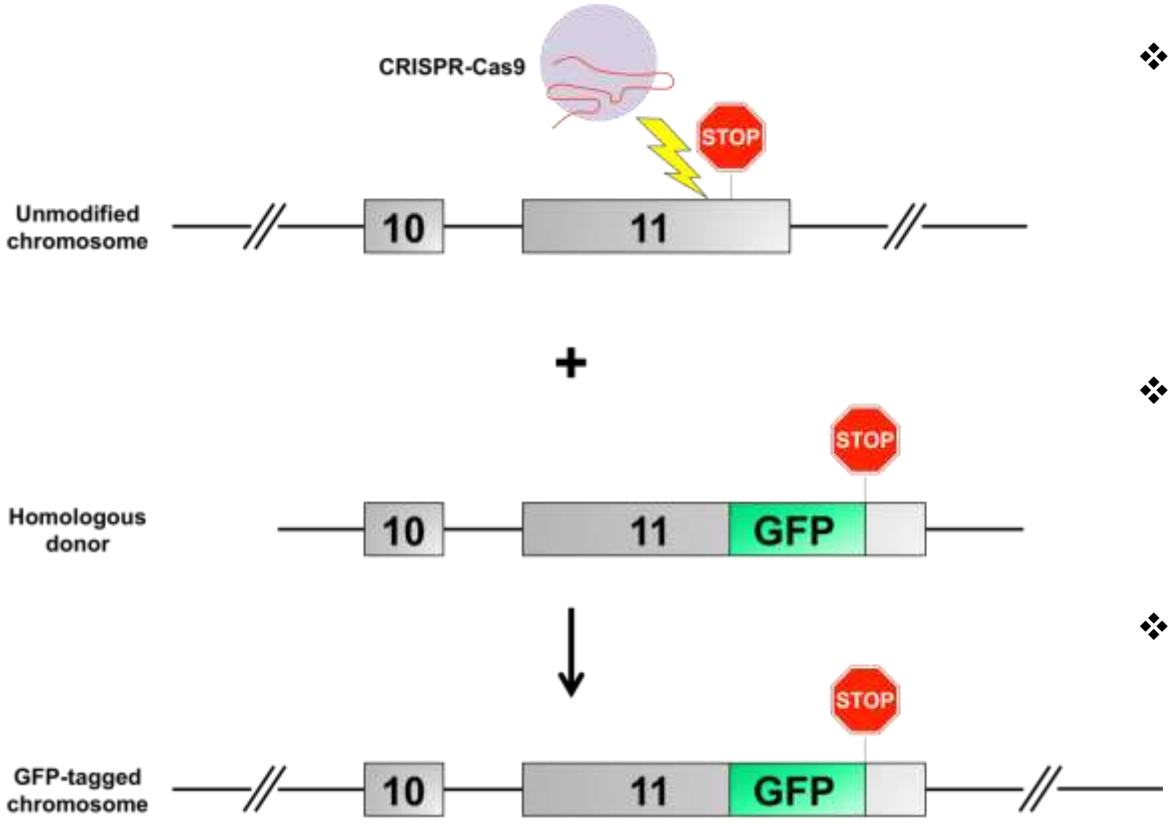
GeneCopoeia genome editing services

CRISPR transgenic mouse services: Case study



- Used CRISPR to create in-frame fusion tag of mouse P2RX2 gene
- Cas9 mRNA + sgRNA + donor DNA injected into pronuclei of sygotes
- Delivered F1 mice carrying modification

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Summary

- CRISPR is a highly effective method for many applications, from knockout, knockin, activation, & more
- CRISPR-Cas9: RNA guided nucleases with some off-target activity, but are very easy to design and use
- GeneCopoeia offers a comprehensive suite of CRISPR products and services ideally suited to meet your genome editing needs, such as:
  - Clone design & construction
  - Kits for validation & screening
  - Cas9 stable cell lines
  - Transgenic mouse services

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Upcoming webinar!

Genome Editing: How Do I Use CRISPR?

Wednesday, February 22, 2017 12:00 pm ET

Register here:

https://attendee.gotowebinar.com/register/9035432894375025411

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Thank you!

If you have any additional questions, please call

1-866-360-9531 x227

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www.genecopoeia.com

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