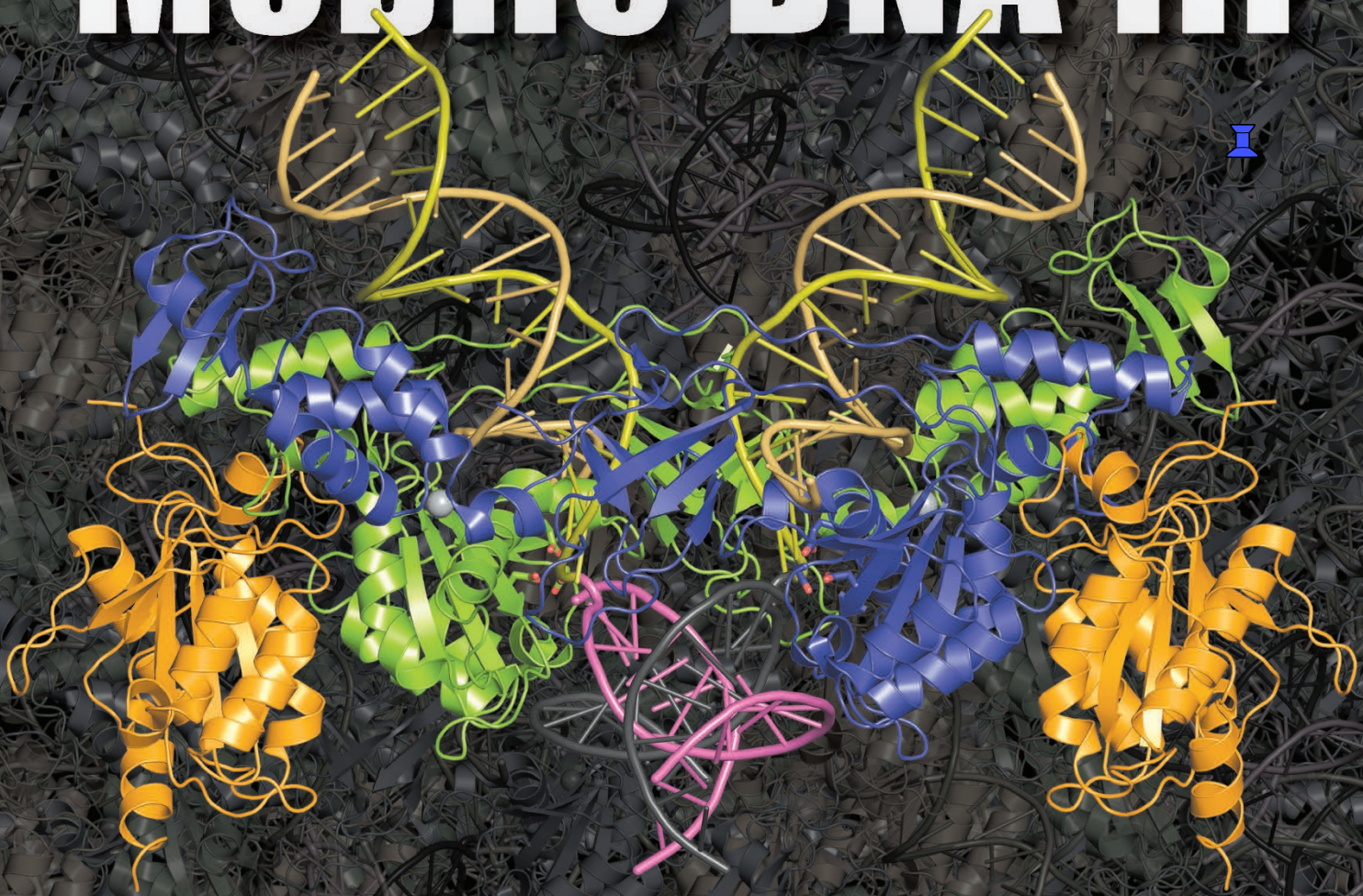
Mobile DNA III



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Cover: An artistic representation of the retroviral intasome engaged with target DNA in the nucleus of a host cell. The illustration is based on the crystal structure of the prototype foamy virus strand transfer complex (Protein Databank ID 3OS0; for details see Maertens *et al*., Nature, 2010, 468, 326-9). Image provided by Dr. Peter Cherepanov, Cancer Research UK, London Research Institute, London, EN6 3LD United Kingdom.

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Preface

Nowhere do the cooperative powers of DNA sequencing, high-resolution protein structure, biochemistry and molecular genetics shine more intensely than on Mobile DNAs. In Mobile DNA II, we knew that almost half of the human genome is comprised of retroelements. What discoveries since Mobile DNA II could surpass that claim? Very simply: everywhere DNA is dynamic, and we now meet the elegant protein machines, co-evolved DNA partners, and diverse RNA choreographers. These pages hold something for every reader, beginning with the introductory overview of mechanisms. Novices will find some of the most lucid reviews of these complex topics available anywhere. Specialists will be able to pick and choose advanced reviews of specific elements, but will be drawn in by unexpected parallels and contrasts among the elements in diverse organisms. Biomedical researchers will find documentation of recent advances in understanding immune-antigen conflict between host and pathogen. Biotechnicians will be introduced to amazing tools for *in vivo* control of designer DNAs. And long-time aficionados will simply fall in love all over again.

Questions still abound about the Transposable Elements (TE) described in this volume. Perhaps none is more profound than the basis and consequences of TE diversity even among related genomes. Active DNA TE show perhaps the most disparate distribution among organisms, being dominant in prokaryotes, and in some animals, including some insects and fish, but with the exception of certain bats, virtually absent in mammals. Plants illustrate expansion of genomes, mediated not only by increasing ploidy, but also by expansion of DNA-based TE and Long Terminal Repeat (LTR) retrotransposons. Although reverse transcriptases are found throughout all kingdoms, autonomous retroelements simply explode together with their non-autonomous partners in mammals with remarkably species-specific types. These differences in mobile DNAs define self and mate, sister species, host and pathogen.

The most striking impression from these pages must be the raw power of genetic material to refashion itself to any purpose. DNA exchange between bacteria and their environment blurs the boundaries between host, transposon, and phage, as organisms secrete and take up DNA, stash genetic material in integrons for future use, conjugate, are attacked by phage and fight back. Delving into mechanisms, we see single-stranded hairpin structures and G quartets that anchor rearrangements in multiple ways; chemically diverse nucleophilic centers–hydroxyls couched in pentose, tyrosine or serine moieties–that covalently bond or attack directly in strand-transfer reactions. Proteins act as clamps to topologically constrain DNA or act as mechanical swivels, linking and unlinking mobilizing strands. Resolution of transposition intermediates might also involve host replication or recombination machinery. More recently discovered helitrons offer unexpected opportunities for expansion of DNA-based elements by rolling-circle replication.

RNA, the primal, catalytic nucleic acid, is in evidence everywhere. In retroelements, RNA partners with reverse transcriptase to deliver on transcriptional expansion of autonomous and non-autonomous TE sequences. Group II introns in bacteria likely gave rise to eukaryotic organelle group II self-splicing, retro-homing introns, Long INterspersed Elements (LINEs), telomerase reverse transcriptases and in addition, spliceosomal introns. Phylogenetic analysis of bacterial genomes previously revealed group II introns, diversity-generating retroelements Diversity-Generating Retroelements (DGR), and retrons, but next generation sequencing now identifies a multitude of novel reverse transcriptases of unknown function.

In ciliates, *Paramecium, Tetrahymena* and *Oxytrichia,* RNA directs massive genome reduction between germ-line and somatic nuclei, mediated by ancient transposase-like enzymes. LINEs containing restriction-enzyme like- or AP-endonucleases dominate in some eukaryotic cells. Others are dominated by LTR retrotransposons and their offspring, the retroviruses; stripped down Penelope-like elements with GIY-YIG endonucleases; DIRS elements with tyrosine recombinases: and attendant non-autonomous elements.

Exceptional elements provide evidence for the interaction of domains over evolutionary time, including LTR retrotransposons encoding envelope proteins, retroviruses replicating intracellularly, and DIRS elements in which retroelement RT/RNaseH is associated with a Crypton-type DNA element tyrosine recombinase.

Nowhere is the sharp focus of structural biology and biochemistry more apparent than in studies of key retroelement enzymes reverse transcriptase and integrase motivated by the quest for inhibitors of human immunodeficiency virus (HIV) replication. Reverse transcriptase structures for multiple retroviruses, as well as now one retrotransposon, demonstrate the robustness of the palm, thumb, fingers model. However, as a caution against too much generalization, subdomains are re-arranged in monomeric, homodimeric, and heterodimeric forms in different enzymes, and catalytic activities operate in *cis* or *trans* within the complex, depending on the enzyme. The structure of full length retrovirus integrase notoriously resisted high resolution structural analysis, but now has rewarded efforts of many labs with key insights (cover of this volume). These include a surprising dimer-dimer interface where active sites are juxtaposed to a trapped, and dramatically bent and widened, major groove target. Whereas LTR retrotransposons target integration to transcriptionally-repressed regions through interactions with heterochromatic protein domains or Pol III-transcribed genes thought to repress Pol II transcription, next generation sequencing has surfaced less dramatic, but significant, retrovirus integration bias, favoring transcriptionally-active regions.

This distribution has been shown now in two cases to be mediated by interactions between integrase and epigenetic mark-associated proteins.

While it has been argued that mobile elements are "selfish DNAs", these pages are replete with examples of the positive contributions of mobile elements to host genome function. Bacterial transposons encode and mobilize selectable markers including antibiotic resistance, detoxifying enzymes, and conjugation and virulence functions. In eukaryotic cells, mobile elements contribute to chromosome structure: constituting centromeres or telomeres in some organisms and seeding heterochromatin in others. TE constitute a large fraction of transcription factor binding sites and provide an ongoing source of novel combinations which are responsive to stress signaling, MAP kinase activation and other developmental signals. Insertions of LINEs and Alu elements affect RNA processing because they encode cryptic splice sites, termination signals, and can target RNA editing.

Exapted mobile DNA coding sequences appear in novel contexts: transposases have evolved into the RAG endonuclease for V(D)J immunoglobulin gene diversification and into heterochromatic factor CENP-B; a reverse transcriptase evolved into telomerase; retrovirus envelope proteins became the trophoblast fusion protein syncytin. There are other examples of TE Open Reading Frames (ORFs) under selection, but with, as yet, unknown functions. Endogenous retroviruses forego prior allegiances and join strategies to resist new infections. For example, Fv–1, a retroviral Gag relic, thwarts incoming retroviruses of similar type. Repeated TE sequences are susceptible to DNA rearrangements via non-allelic recombination, aborted transposition, and generation of pseudo-genes–all of which might ultimately contribute to the resiliency of host genomes.

TE exploit their hosts as well. The bacterial XerCD tyrosine recombinases which function in bacteria to unlink multimeric chromosomes are exploited to integrate phage genomes or mediate invasion of the host chromosome on behalf of certain plasmid-borne mobile elements. Transposases, resolvases and integrases *in vivo* likely associate with host factors as they are joined with host genomes. TE are generally tightly controlled by host regulation so that some display opportunistic bursts of activity during specific windows of development. This is exemplified by yeast Ty transcription in response to MAP kinase signaling and activation of reverse transcription by DNA checkpoints. A common theme more generally is TE activation during stress. Diverse retroelements are derepressed during periods of germ cell development ensuring their vertical spreading in populations.

Despite these examples of cooperation, mobile DNAs are also in conflict with their hosts. RNA interference likely arose in part to combat mobilization of retroelements. Invaders of one sort or another engage in a dizzying unscored dance with their hosts. One result of this conflict is rapid evolution of genes encoding host innate immunity restriction factors, which for retroviruses include ones that prematurely uncoat incoming viruses, starve reverse transcriptases for nucleotides, and deaminate cytidines in replicating cDNA. Some of these same factors also suppress movement of endogenous retroelements.

Programmed variation is used by invaders and hosts alike for purposes of immune evasion or resistance, respectively. Examples include *Salmonella* Hin invertase flipping a promoter sequence to switch between expression of different antigenic flagellar proteins and DGR directing mutagenic reverse transcription of a template transcript coupled with directed conversion of a target expression site. *Neisseria gonorrhea, Borrelia burgdorferi*, *Trypanosoma brucei*; and *Plasmodium falciparum*, agents of gonorrhea, Lyme disease, sleeping sickness, and malaria, respectively, use amazingly diverse mechanisms to program variation of their antigenic surfaces for immune evasion. To counter this assault, there

is programmed variation of host immune proteins. In human immunoglobulin production, a DDE TE-derived RAG site-specific endonuclease initiates V(D)J switching, followed by transcription-activated somatic hyper-mutation (activation-induced cytidine deaminase), nuclease introduction of DSB, and final joint formation by redundant NHEJ pathways.

Next generation sequencing and development of methods for rapid TE mapping have greatly improved understanding of the distribution of TE as well as the utility of transposons for functional genomics. The bacterial Tn5 system has been exploited in particular for *in vitro* mutagenesis and next generation sequencing libraries by collapsing fragmentation and adapter ligation into a single step. P, Hermes, piggyBac, and Sleeping Beauty transposons have wide activity in eukaryotic systems and have been harnessed for genome-wide profiling, gene disruption and tagging, and genome modification. Retroviruses are additionally used in lineage tracing. The controlled, high-frequency mobilization of Mutator has made it indispensable for gene discovery in maize.

In medical research, understanding the impact of DNA mobilization is critical. In addition to individual TE, other mobile DNAs such as plasmids, Integrative Conjugative Elements (ICE) and both transposon-borne and chromosomal integrons are bacterial reservoirs of mobilizable antibiotic resistance. HIV, malaria, and sleeping sickness, and other pathogens, too numerous to mention here, remain threats to global health. Mobile element vectors transposons piggyBac, Sleeping Beauty, lenti-retroviruses and adenoviruses are being used as vectors to introduce exogenous DNAs in research, and in clinical trials. They differ with respect to targeting, excision footprints, payload size, and host activity profiles. Their mechanisms of DNA breakage and joining were among the systems first analyzed, now enabling them to be harnessed and used extensively for genome engineering including with developmentally-regulated expression, inactivation, and self-deletion strategies to enable probing essential or tissue- specific functions.

What challenges remain? One goal is to connect key findings from basic research, to clinical developments in drug resistance and genetic engineering. This volume is based on the considerable increase in understanding of molecular mechanisms of mobilization in the last decade. However, we have likely seen only the tip of the iceberg of how mobile DNAs affect the day to day biology of their hosts.

In the human genome alone, retroelements provide promoters for long non-coding and other RNAs of completely unknown function; Alu elements redirect RNA processing and delivery, and mobilization is occurring during neuronal development and in cancer with unknown consequences, just to mention a few. Finally, endogenization of a gamma retrovirus in Australian koalas is ongoing and those studies should provide insights into retroelement-host interaction. How have transposition events after separation from other great apes contributed to traits that make us human? What transposition events will provide key substrates for future evolution? And of course, perhaps the ultimate question, could we survive as a species were there no transposition?

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Introduction

I

Mobile DNA, 3rd Edition
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A Moveable Feast: An Introduction to Mobile DNA

INTRODUCTION

DNA has two critical functions: to provide the cell with the information necessary for macromolecular synthesis and to transmit that information to progeny cells. Genome sequence stability is important for both these functions. Indeed, cells devote significant resources to various DNA repair processes that maintain genome structure and repair alterations that can arise from DNA synthesis errors and assaults from both endogenous and exogenous sources. DNA sequence variation, however, provides the substrate for adaptation, selection, and evolution.

Genomes are, however, highly dynamic. Notably, they vary not only at the single or several base pair level (although such changes can be transformative and even deadly), but they also change by DNA rearrangements, that is, the movement of DNA segments that may be many kb (or even longer) in length. Such rearrangements can have enormous impacts on genome structure, function, and evolution.

The DNA rearrangements discussed here generally involve specific DNA sequences, or in some cases RNA sequences, that are recognized and acted on by specialized recombination proteins or recombinases that promote DNA breakage followed by joining of the broken DNAs to new sites. The involvement of a sequence-specific recombinase is what distinguishes site-specific recombination from homologous recombination, which can occur between any two DNA segments as long as they are homologous to each other, as in RecA- and Rad51-dependent recombination. In some cases, the specialized recombinase is a sequence-specific nuclease that targets homologous recombination to a specific DNA site.

In some rearrangements, the recombinase alone breaks, exchanges, and joins DNA by using covalent protein-DNA intermediates. In other cases, DNA synthesis is also essential in these rearrangements. Notably, this DNA synthesis can involve not only conventional DNA synthesis in which a DNA polymerase uses DNA as a template, but also reverse transcription in which a novel DNA polymerase, reverse transcriptase, uses an RNA template to generate new DNA. A very wide number of other cellular processes can influence or be required for DNA rearrangements, including transcriptional activation of particular sites, DNA bending by bending proteins, DNA supercoiling, and many variations in chromatin structure, as well as DNA repair reactions including DNA end joining. Although a purified recombinase may execute DNA breakage and joining *in vitro*, it is critical to remember that this reaction and its consequences will be enormously influenced by its cellular environment.

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Although DNA rearrangements can provide very useful rapid and focused changes in genetic information, they are also very hazardous. Unrepaired DNA breaks can result in DNA mis-segregation and are often lethal. Not surprisingly then, DNA rearrangements often occur in elaborate nucleoprotein complexes that organize and juxtapose the participating DNAs and promote breakage and joining in carefully choreographed steps. The frequency of DNA rearrangements is usually highly regulated, often by restricting to low levels the recombinase that initiates or mediates the rearrangements.

Mobile DNAs also include a diverse variety of discrete mobile genetic elements, such as transposable elements, that move themselves or copies of themselves from place to place within and between genomes. Thus, in some cases, a copy of the element remains at its original site and there is a new copy at the new insertion site. This type of replicative mechanism leads to an enormously high element copy number, especially in some eukaryotic genomes. The majority of the maize genome, for example, is derived from a particular kind of transposon. High copy numbers of repetitive sequences result in increased susceptibility to nonallelic homologous recombination events that can lead to deletions, inversions, translocations, and other chromosomal rearrangements.

The movement of a transposable element within a single genome can have substantial genotypic and phenotypic consequences. The insertion of a transposable element into a gene can lead to gene disruption but even nearby insertions can effect gene expression as many elements carry regulatory signals, such as enhancers and promoters, as well as splice sites and transcription termination signals. Excision of an element also changes the donor site. Thus, the intracellular translocation of a mobile element results in genetic variation. The range of target sites used by the elements ranges from insertion into specific sites or regions that provide a "safe harbor" for the element with reduced negative consequence on the host, to preferences for actively transcribed regions to facilitate element expression to virtually random insertion, which can thus result in genetic variation anywhere within the host genome.

DNA rearrangements also play a crucial role in the interactions between viral chromosomes and their hosts, as well as the proper replication and segregation of host chromosomes. Many viruses integrate into and excise from host genomes, although in some cases integration is irreversible, such as with HIV-1. All of these reactions involve at least specific sites on the viral genome that are acted upon by site-specific recombinases and which sometimes involve specific sites on the host genome. Recombination between specific sites to promote chromosome monomerization plays a key role in chromosome transmission in bacteria.

The translocation of mobile elements encoding a wide variety of determinants including genes encoding antibiotic resistances, virulence determinants, and diverse metabolic pathways from plasmids to chromosomes and from viruses and DNA fragments that are transduced or transformed into a cell, can also result in permanent chromosomal acquisition of these determinants. This sort of horizontal gene transfer involving mobile elements is rampant in bacteria and contributes greatly to genetic variation. There are also an increasing number of examples of horizontal gene transfer involving mobile elements in eukaryotes.

Perhaps the most profound example of the effect of mobile elements on eukaryotic genome evolution is the nuclear invasion of mobile group II introns into the nuclear genome from bacterial symbionts to form spliceosomal introns.

Cell type can also have substantial impact on DNA rearrangements. The elaborate DNA breakage and joining reactions that underlie immunoglobulin diversification are actually terminal differentiation events restricted to particular somatic cells. There is increasing interest in the somatic movement of transposable elements, which can also have profound organismal impact. The movement of human transposable elements in somatic tissue is associated with a variety of cancers, although it remains to be determined if such events can cause oncogenic transformation or are rather a consequence of transformation. The movement of transposable elements in neuronal tissue in several organisms raises the interesting possibility that such rearrangements are a deliberate strategy for neural plasticity.

Such terminal differentiation events involving DNA rearrangements are incompatible with the bacterial lifestyle, except in a few known cases such as spore formation by a subset of cells. By contrast, reversible DNA inversions that vary promoter or ORF orientation are well known in bacteria.

Thus, DNA rearrangements can contribute substantially to genetic variation. The frequency and potential advantage of the resulting variation must be carefully balanced with genome stability to avoid its potential for population-wide genomic catastrophe.

Although not exclusively so, the focus of this work is on the mechanism and regulation of DNA rearrangements. How do specific DNA (and sometimes RNA) sequences recognize each other and how do they assemble to form the machines in which DNA rearrangements occur? What are the mechanisms for DNA

strand breakage and joining? What processes determine when and where these reactions occur? How are actions at multiple DNA sites, for example, the two ends of a transposable element and its target DNA, coordinated? Importantly, how are nonproductive breakage and joining events avoided and how is intact duplex DNA regenerated?

Mobile DNAs are "natural" genome engineers. Although not a focus of this work, many of the mobile elements discussed here have been harnessed to facilitate researcher-directed rearrangements both *in vitro* and *in vivo*. Mobile elements are used for "random" insertional genome mutagenesis both *in vivo* and *in vitro*, as well as for "targeted mutagenesis." Many mobile elements are used as vectors in both homologous and heterologous systems.

TARGETED DNA BREAKS LEAD TO GENE REPLACEMENT

DNA Double Strand Breaks Stimulate Homology-Dependent DNA Repair

Homologous recombination occurs without requirement for any particular sequence, depending only on base pairing between the participating DNA strands. However, the frequency of homologous recombination is stimulated by the presence of broken DNA, in particular double strand breaks. These breaks stimulate recombination because the action of nucleases and helicases at these breaks leads to the generation of DNA with single stranded 3′ trails that are the preferred substrate for DNA pairing mediated by RecA- and Rad51-like proteins. By interacting with a donor site, this pairing of 3′-OH ends can initiate homology-dependent DNA repair, which copies DNA sequence information from the donor site into the broken DNA target site. This repair leads to the replacement, or modification, of an existing gene or insertion of a new gene. The insertion of many mobile DNAs into a new site is targeted by double strand breaks by highly site-specific endonucleases.

There's No Place Like Home: Homing Endonucleases

Homing endonucleases (HENs) are highly site-specific endonucleases (1). Although often associated with other genetic elements (see below), freestanding HEN genes can themselves be mobile DNA elements. If a HEN cleavage site lies within an "empty allele" of DNA that flanks the HEN ORF, cleavage of that target site can initiate homology-dependent DNA synthesis that will transfer a copy of the HEN gene to that double strand break at the nuclease target site (Fig. 1).

HEN genes are also often found in other genetic elements such as self-splicing RNA introns, that is, group I introns, and self-splicing proteins, that is, inteins. Thus, if the HEN introduces a double strand break into the "empty" allele of a site occupied by the intron or intein, targeted DNA repair introduces a copy of the DNA encoding the intron or intein into that target site. Because the RNA intron can splice out of the RNA containing it and the protein intein can splice out of the protein containing it, the insertion of these elements is generally phenotypically silent.

Alternative Life Styles: Switching Mating Type in *Saccharomyces cerevisiae*

These yeasts have two different haploid cell types, mating type **a** and mating type α, which can mate to form diploids. During sporulation, meiotic recombination shuffles the two parental genomes, generating diverse haploid progeny. To facilitate diploid formation, haploids can switch mating type from mating type **a**

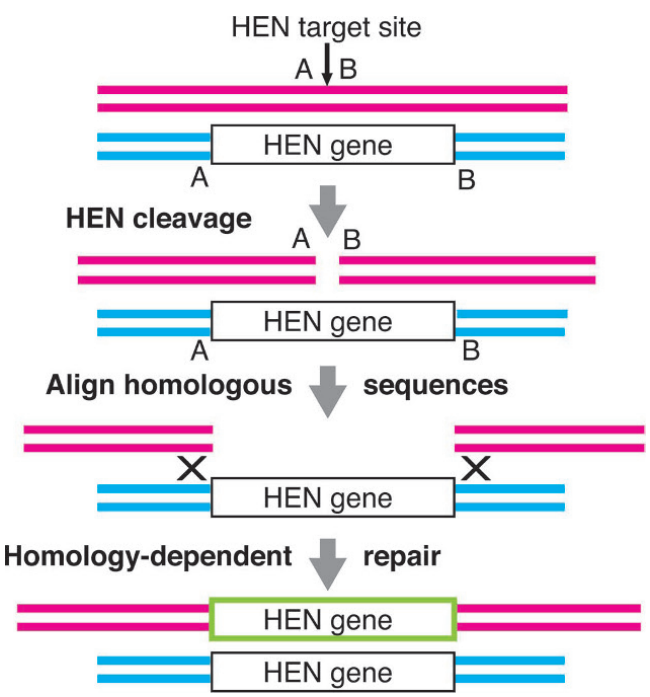

Figure 1 A targeted DNA double strand break can lead to gene insertion. Introduction of a site-specific double strand break by a homing endonuclease (HEN) in a homologous DNA duplex lacking the HEN gene targets homology-dependent DNA synthesis (green) that introduces a copy of the HEN gene to the broken DNA.
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