Method To Implement A Crispr-Cas9 Copycat Gene Drive In Rodents

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BACKGROUND

Currently, alleles at multiple loci in the mouse genome must be combined by Mendelian genetics in crosses of animals to one another to produce a desired compound mutant genotype. For example, to combine homozygous mutations at two loci, animals that are heterozygous for each gene must be produced by breeding, and these are subsequently crossed to one another. Since the frequency of homozygosity for each allele is 1:4 the frequency of homozygosity for both genes is 1:16. Since the average litter of mice is approximately 10 pups, and the generation time from conception to reproductive age is about 3 months, this requires a substantial number of animals and time. With the addition of each new locus (three, four, etc), the cost measured in animals, time, and money increases exponentially. These factors increase substantially more if two or more loci are genetically linked, which requires rare recombination events to combine engineered alleles on the same chromosome.

The CRISPR-Cas9 gene drive system stands to revolutionize rodent breeding. If each desired allele is encoded as a gene drive element that contains an sgRNA designed to target the same genomic location in the wild type homologous chromosome, each locus will be “driven” to homozygosity in the presence of Cas9. Therefore, in order to combine three alleles, for example, a mouse with one gene drive element (A) would be crossed to a mouse that encodes Cas9. Offspring of this cross would then be crossed to mice carrying gene drive element B, and these offspring would be crossed to mice carrying gene drive element C. In the presence of Cas9 at each generation, these gene drive elements at three distinct loci will be converted to homozygosity such that 50% of offspring, those that inherit Cas9, will be triple homozygous after three generations, even if they are genetically linked loci.

A CRISPR-Cas9 mediated gene drive leverages the native cellular mechanism of homology directed repair to copy a desired allele from one chromosome to another. This process can convert a heterozygous genotype to homozygosity in a single generation. While CRISPR-Cas9 gene drives have been implemented in two species of insects, flies and mosquitos, it has not been reported in any non-insect animal species.

TECHNOLOGY DESCRIPTION

Researchers at UC San Diego have a developed a method to use CRISPR-Cas9 gene drive in rodents, notably mice and rats that are research and commercial models of human physiology and disease.

APPLICATIONS

A CRISPR-Cas9 mediated gene drive is a method that leverages the native cellular mechanism of homology directed repair to copy a desired allele from one chromosome to another. This process can convert a heterozygous genotype to homozygosity in a single generation.

ADVANTAGES

Once the efficiency is optimized in mouse models using our reporter animal, the method can be implemented in a wide variety of applications to model disease, test drug efficacy and metabolism, and potentially to control wild rodent populations.

STATE OF DEVELOPMENT

The invention is at the experimental data stage, although proof of concept has been completed.

INTELLECTUAL PROPERTY INFO

The invention is patent pending and available for licensing.

PATENT STATUS

Country	Type	Number	Dated	Case
Patent Cooperation Treaty	Published Application	2019140064	07/18/2019	2018-176

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OTHER INFORMATION

KEYWORDS

Gene drive, CRISPR-Cas9, genetically modified rodent, disease models

CATEGORIZED AS

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