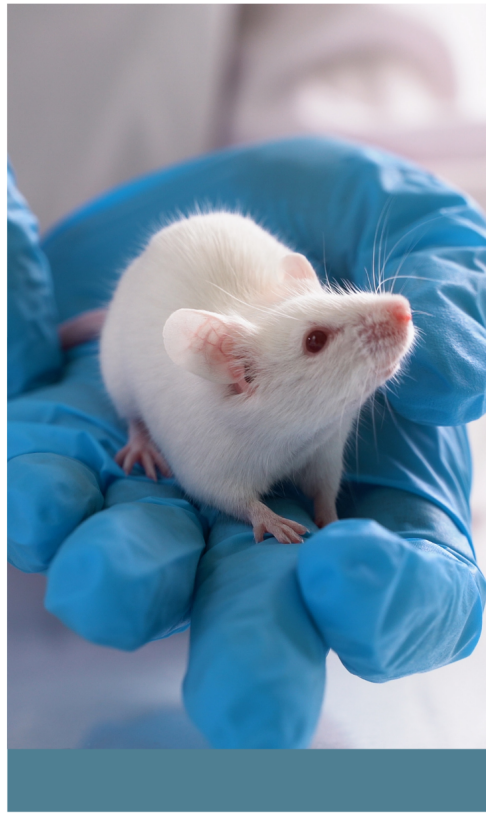
ers GENOMICS
Your connection to CRISPR/Cas9

CRISPR/CAS9 ANIMALS:
EXPANDING THE ANIMAL GENOMICS WHEELHOUSE

OVERVIEW



CRISPR/Cas9 has revolutionized the field of genome editing. This system has demonstrated an unprecedented efficiency, multiplex-capability, and ease of use not previously available. Some of the recent advances include genome-wide screens in model organisms, accurate models of human diseases and potential therapies being validated in humanised animal models (Kato and Takada, 2017). CRISPR/Cas9 reduces the time and cost required for genome editing and enables the production of animals with extensive genetic modifications. It is applicable to a wide variety of animals, from early-branching metazoans to primates. Several achievements in genetic modification of animals have also been translated into products for the agricultural and pharmaceutical industries.

Based on the remarkable progress to date, CRISPR/Cas9 technology has enabled advances including:

- Manipulating animal models to help further understand the basis of diseases with complex genetic origins (Kato and Takada, 2017).
- Engineering animals to produce proteins, cell lines and humanized organs for research and potential transplantation
- Genetically protecting populations of animals in agricultural settings to prevent the spread of disease.

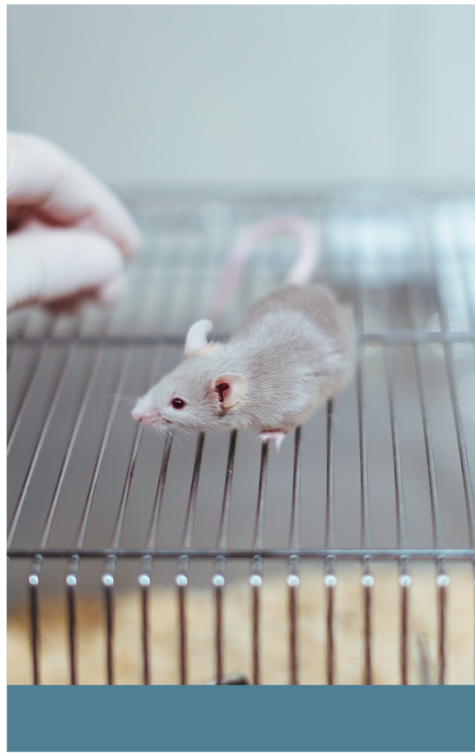
There are several methods of producing genetically modified animals such as through:

- Germline editing via injection or electroporation of CRISPR/Cas9 reagents into early-stage zygotes or gonads, as used in model organisms such as worms, zebrafish, and fruit flies;
- Primary cell editing followed by somatic cell nuclear transfer (SCNT), often used in larger animals, such as pigs and cows; and
- Blastocyst injection with genetically modified embryonic stem cells followed by breeding to produce stable germline mutants, traditionally used in rodents. CRISPR/Cas9 reagents can be introduced in the form of plasmids, mRNA, or as a Cas9 protein + guideRNA complex, or even via viral vectors such as AAV.

The uses of CRISPR/Cas9 for animal genome engineering has a multitude of applications such as:

- The inactivation or alteration of genes in model animals in order to elucidate the functions of these genes.
- The production of animal models of human disease to study disease progression in a controlled manner and evaluate potential therapies and;
- The use of genetically modified animals for industrial, pharmaceutical, and biotech production.

DISEASE MODELLING:



Mouse models of human genetic traits, development, and diseases have been utilized broadly in basic and applied research. One particularly important application of disease modelling using CRISPR has been in recapitulating the onset and progression of various cancers. A group at MIT/Broad Institute used CRISPR/Cas9 in neurons, cells of the immune system, and endothelial cells to model the role of three genes whose mutations are associated with initiation and progression to lung cancer, namely K-Ras, TP53, and LKB1. These groups were able to deliver CRISPR/Cas9 using a variety of means, including AAV and lentivirus (Platt RJ et al., 2014). Another team used hydrodynamic tail-vein injection to deliver CRISPR/Cas9 reagents to the mouse liver in vivo to target and disrupt the tumor suppressor genes PTEN and TP53 both alone and in combination (Xue W et al., 2014). This team showed that the resultant inactivation of these genes in vivo led to cancerous tumors.

FARMING:

Gene editing using CRISPR/Cas9 has impacted industrial production by accelerating the creation of animals with novel genotypes that may be beneficial for agricultural production. For example, the company AgGenetics has engineered Aberdeen Angus cows—the cows that are bred for Angus beef—to produce short white hair, which is better suited for warmer climates (Patel M., 2017). This could enable Aberdeen Angus herds to thrive in a broader range of environmental conditions, and thus increase the agricultural potential of Angus beef.

PHARMACEUTICAL PRODUCTION:

Genetically modified animals have already been used in the production of recombinant proteins for pharmaceutical use. For example, the company GTC Biotherapeutic engineered goats (using pre-CRISPR/Cas9 methods) to produce antithrombin and secrete this pharmaceutical agent in their milk. The Pharmin Group has engineered transgenic rabbits to similarly produce and secrete a C1-esterase inhibitor. Although these examples have demonstrated that transgenic animals can be excellent sources of recombinant pharmaceuticals, this strategy has been difficult to generalize due to technical challenges. It is clear that the ease of use and efficiency of CRISPR/Cas9 will expedite the production of new animals as "bioreactors" for pharmaceutical production with several companies already having programs underway. (Zou Q et al., 2015)

COMPANION ANIMALS:

Genetically modifying pets to produce healthier breeds, as well as introducing custom traits, has been on the agenda of the gene editing field for several years. Many pure dog breeds suffer from a variety of conditions related to the limited gene pool required to maintain such purebred stock. Many of these negative traits are addressable through genome editing and can be used to maintain a healthier breeding stock. CRISPR/Cas9 has been used to produce dogs with improved running ability by inactivating MSTS, a negative regulator of skeletal muscle mass (Zou Q. et al., 2015). Very small pigs (often called "micropigs") have been produced using CRISPR/Cas9 and advertised as pets. (Cyranoski D., 2015) Plans are underway to use gene editing technology to design custom coat patterns in some domestic animals. (Reardon S. 2016)

As the global licensing leader for CRISPR/Cas9, ERS Genomics is the first port of call when developing a commercial or research application using CRISPR/Cas9. This applies whether you're a new biotech start-up or an established life sciences organisation.

We have already completed more than 100 licence agreements across a range of life science sectors and make patent rights available in more than 80 countries – the most comprehensive collection of proprietary rights to CRISPR/Cas9 available.

Talk to us today to discuss your licensing needs and let our experienced team help you to leverage the power of CRISPR/Cas9.

CONCLUDING REMARKS

CRISPR/Cas9 technology has enabled and accelerated the creation of a wide range of animals and this has led to discoveries and innovations throughout basic and applied science. CRISPR/Cas9 technology has not only contributed to expand the number of animals that are tractable for genome modification, but has also enabled the generation of highly sophisticated genotypes. In view of the impressive achievements already made in the last few years with this technology, we expect to see many novel discoveries and products involving genetically modified animals in the coming years.

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