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Efficient animal model generation using zinc-finger nucleases and CRISPR/Cas systems

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Genetically modified animal models have been powerful tools for studying gene functions and human diseases. Over the past two decades, the predominant gene-modified animal models have been mouse models largely because the mouse embryonic stem cell-based genome editing technology was the primary method to create precise gene modifications in animals. The development of engineered nucleases has not only accelerated animal model production but also expanded animal models to numerous species or organisms other than the mouse. Engineered nucleases create double-strand breaks (DSBs) at targeted genomic loci, which can be repaired either by non-homologous end joining (NHEJ) or by homology-directed repair (HDR). Since 2009, our Lab (Horizon Discovery, formerly SAGE Labs) has been using zinc-finger nucleases (ZFNs) to create hundreds of genome engineered mouse, rat and rabbit models by direct pronuclear microinjection. While ZFN-based gene editing was efficient and specific, the time-consuming ZFN engineering has hampered the further extensive application of this technology. In recent 5 years, we have primarily used CRISPR to create genetically engineered animal models. We found that while both ZFN and CRISPR are equally efficient in creating different types of rat models, CRISPR is more efficient in HDR-based mouse model generation. After continuing optimizations, we have established methods to achieve highly efficient genome editing with relatively low off-target effect. We will present some case studies to show ZFN and CRISPR/Cas system-mediated point mutations, targeted integrations, megabase deletions as well as some challenges in an animal model generation.

Biography

Guojun Zhao has been working in in vivo genome editing since 2011. He joined Sigma-Aldrich (SAGE Labs) in 2011 and since then he has been using ZFNs and CRISPR/Cas systems to create hundreds of genetically engineered mouse, rat and rabbit models for customers worldwide. Those animal models help scientists in big pharma companies and universities study gene functions and find methods to control human diseases.

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