CENTER FOR THE DEVELOPMENT OF NEW MODEL ORGANISMS

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Since the beginning of life on Earth, living organisms have evolved to adapt to various environments, and have spawned a wide variety of species. Modern biological research has put an emphasis on elucidating the basic principles common to many species, and has progressed thanks to the intensive analysis of species known as model organisms, which are easy to handle in a laboratory environment. However, this development has left many interesting biological phenomena unexamined as their distinctive characteristics are observed only in a particular group of species of model organisms. How we overcome this problem is an important challenge for biology hereafter.

To solve this problem, we need to choose species most suitable to analyze the phenomena of interest, and then establish them as new model organisms by developing new methodologies. These include stable raising, breeding and experimental manipulation techniques, analyses of the genome information and gene expression, and gene manipulation techniques using gene insertion and genome editing techniques.

To this end, The Center for the Development of New Model Organisms was established in 2013 and through its activities; organisms that have been rarely used in research have been recently designated as new model organisms, including aphids and sea anemones, to understand symbiosis phenomena or rhinoceros beetles for studying the evolution of the insects. We are refining various processes ranging from information sharing regarding new model organisms to the development of genetic and phenotype analysis and genetic engineering, and aim to seamlessly fashion these steps into a continuous research flow.

Research activity by K. Suzuki

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Two technical innovations have recently changed biology: Next Generation Sequencing (NGS) and Genome Editing. NGS reveals whole genome sequences and gene expression profiles from various organisms. Genome Editing accelerates the functional characterization of numerous genes involved in a variety of phenomena of life. Accordingly, we are now basically able to choose any organism which we are interested in, and carry out functional analyses by using these tools.

I. Development of genome editing techniques for various organisms.

Recent advances in the CRISPR-Cas system now allow for reverse genetics in various organisms. However, it has been hampered by the lack of a simple and efficient method for gene modification in most of the non-model organisms. To overcome this problem, we developed a highly-efficient workflow for gene knockout in the founder using this CIRSPR-Cas. We call the virtually knockout founders “crispants”. Crispant assay provides us with a practical and rapid tool for functional screening of numerous genes of interest beyond the post-genome era (Figure 1).

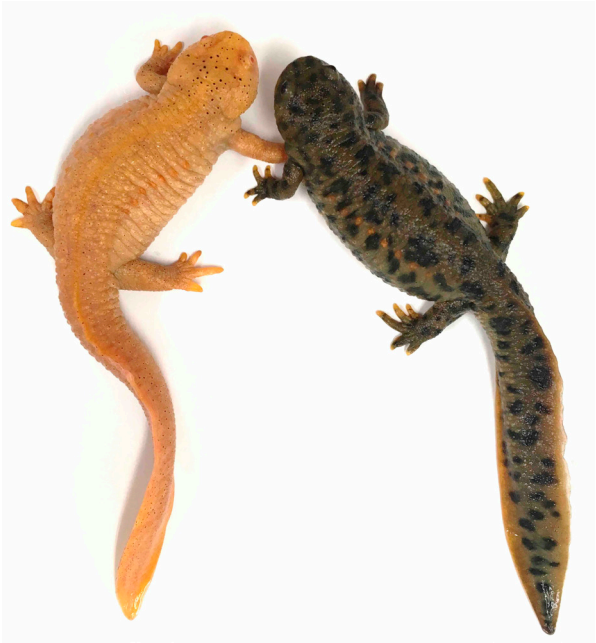

Figure 1. *tyrosinase* crispant in *P. waltl*. A knock-out founder of tyrosinase, a melanin synthesis enzyme, and wild newt (left and right, respectively). *tyr* crispant shows full albinism.

Despite the practical utility of the knockout technique, there is still room for improvement in the integration of exogenous DNA into a target chromosomal site (*i.e.* knock-in), which is still somewhat limited in various organisms. Therefore, we are currently developing more efficient and practical knock-in techniques than conventional ones.

II. Finding new model organisms and deciphering organ regeneration

One of our missions is to discover unique organisms and develop them as new model organisms for basic biology. A recent example of this is our recent establishment of the newt *Pleurodeles waltl* as an experimental model animal for regenerative biology using NGS and Genome Editing techniques. *P. waltl* possesses several excellent characteristics as a model animal: easy breeding, short sexual maturation period, remarkable regenerative capacity and comparatively high efficiency of genome-editing (Figure 2). We are currently investigating the molecular basis of organ regeneration using this newt. In addition, we widely support researchers who attempt to develop new model organisms contributing to up-coming biology.

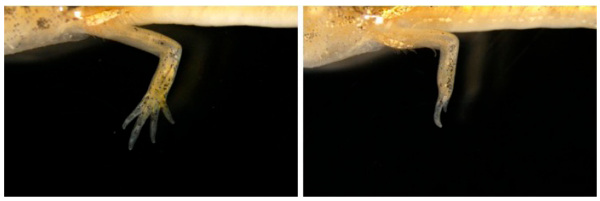

Figure 2. A limb-specific enhancer (ZRS/MFCS1) of *sonic hedgehog* crispant in *P. waltl*. Phenotypes of limb regeneration in wild and ZRS/MFCS1 crispant (left and right, respectively). Unlike in normal limb regeneration in the wild type, severe reduction of digit formation was seen in ZRS/MFCS1 crispant.

Publication List:

〔Original paper〕

- Suzuki, M., Hayashi, T., Inoue, T., Agata, K., Hirayama, M., Suzuki, M., Shigenobu, S., Takeuchi, T., Yamamoto, T., and Suzuki, K. (2018). Cas9 ribonucleoprotein complex allows direct and rapid analysis of coding and noncoding regions of target genes in *Pleurodeles waltl* development and regeneration. Dev. Biol. *443*, 127-136.

〔Review article〕

- Suzuki, K., Sakane, Y., Suzuki, M., and Yamamoto, T. (2018). A simple knock-in system for *Xenopus* via microhomology mediated end joining repair. Methods Mol. Biol. *1865*, 91-103.