Technology Offer

High-precision base editors for site-specific single nucleotide conversion

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Background

The CRISPR-Cas system is a powerful tool for site-specific genome editing. It allows for the inactivation or substitution of entire genes. However, most hereditary diseases in humans are caused by single point mutations, the correction of which requires only subtle changes to the DNA. Recently, base editors (BEs) were developed that allow the introduction of selective nucleotide substitutions. A Cas9 enzyme is fused to a nucleobase deaminase catalysing C-to-T mutations (by C-to-U deamination) or A-to-G mutations (by A-to-I deamination). Such BEs have enormous potential in genome editing, gene therapy and precision breeding.
Yet, current BEs suffer from limited specificity in that they edit different and/or multiple nucleobases within the activity window, defined relative to a PAM (protospacer adjacent motif) sequence. For broad application, especially in human therapies, improved systems will be needed that provide extraordinary accuracy of site-specific editing, ideally without any off-target effects.

Technology

Researchers from the Max-Planck-Institute of Molecular Plant Physiology in Golm invented high-precision C-to-T BEs with narrow activity windows that can selectively edit a single nucleobase at a specific position with high accuracy and high efficiency (1). The scientists hypothesized that structural flexibility between the Cas9 module and the deaminase module caused the observed inaccuracies of previously designed BEs, and decided to engineer the connection between the modules. The use of rigidifying linkers and/or the truncation of non-essential and flexible protein parts resulted in new fusion proteins that show a strong increase in editing precision while maintaining full deaminase activity.
In subsequent experiments, the scientists adapted this strategy to various Cas9 and deaminase variants and established an entire BE toolbox (2).
The toolbox allows for the selection of the most suitable BE based on three criteria:

(1) the nature of the PAM sequence: the Cas9 moiety was engineered to recognize alternative PAM sites,

(2) the specific C to be edited: selective targeting of sites -19 to -14 is possible, and

(3) the presence or absence of bystander Cs: some of the new BEs tolerate a C in close proximity to the target C, while still maintaining high editing precision.

The BEs of the toolbox combine superior editing precision with high editing efficiency and product purity, and will be widely applicable in many areas of basic and applied research.

We are seeking licensing partners for the further development and exploitation of this technology.

Patent Information

A PCT application was filed in January 2020.

Literature

(1) Tan, J. et al., Nat. Commun. 2019, doi: 10.1038/s41467-018-08034-8

(2) Tan, J. et al., Nat. Commun. 2020, doi: 10.1038/s41467-020-14465-z

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