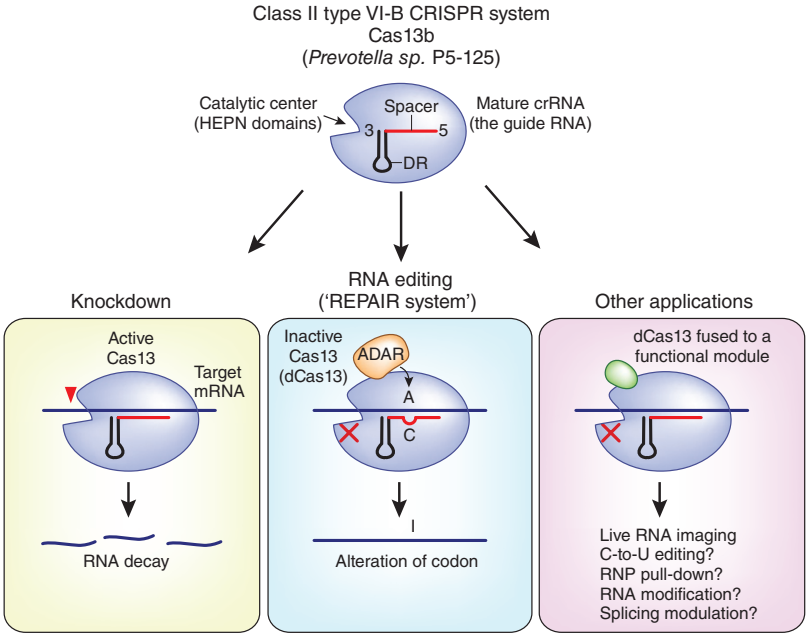

Figure 1 Cas13 as a versatile tool in RNA research. Cas13b associates with crRNA (the guide RNA) to form a gene-specific effector complex. Cas13b contains a composite catalytic center that is formed between the intramolecular dimer of two HEPN domains (indicated with an arrow). crRNAs have a common direct repeat (DR) and a spacer that base-pairs with the target. Wild-type Cas13b induces specific knockdown (bottom left). A catalytically dead dCas13b is fused to ADAR which confers A-to-I editing activity. An adenosine in an A-C mismatch of RNA duplex is edited preferentially by ADAR (bottom middle). Hence, we can expect that the fusion of dCas13 and heterologous functional modules will offer many interesting applications in the not-too-distant future (bottom right). RNP, ribonucleoprotein.

RNA-binding activity so as to avoid off-target editing. One such mutant (ADARDD) fused to dCas13b achieved high specificity toward the intended sites as well as relatively high frequency (10–40%) of editing. ADAR mutants preferentially deaminate adenosine mispaired with cytidine in RNA duplexes, which is exploited to enhance precise base editing by introducing A-C mismatch to the guide-target duplex region. ADAR induces the conversion of adenosine to inosine which is equivalent to guanosine in translation and splicing. This technique, referred to as "RNA editing for programmable A-to-I replacement" (REPAIR) can indeed repair disease-relevant G>A nonsense mutations in cell culture, including *AVPR2* W293X (878G>A) found in X-linked nephrogenic diabetes insipidus and *FANCC* W506X (1517G>A) associated with Fanconi anemia. Thus, this study shows a possibility for programmable RNA editing as a new therapeutic avenue, although any therapeutic applications will clearly warrant further improvements of the technique.

Moreover, this dCas13b platform is likely to offer ample opportunities to create new tools for RNA research. It will be interesting to test in the future if C-to-U editing is plausible when APOBEC is used instead of ADAR. The emerging field of epitranscriptomics will also benefit from versions of Cas13 that allow manipulating epitranscriptome marks directly by fusing Cas13b to RNA-modifying enzymes such as methyltransferases.

What's more, many other regulatory factors, such as splicing factors, translation factors, or localization factors, could also be studied with appropriately designed Cas13 variants. Thus, fusion proteins may be useful in correcting pathological misregulation as well as in investigating the biological functions of the regulatory factors.

Live RNA imaging is another area to which dCas13 can contribute greatly. The same group previously demonstrated that fluorescence protein fusion to dCas13 can be used to track cellular RNAs in real time[1]. Moreover, dCas13 may be engineered to harbor tandem tags for purification of RNA–protein complexes and identify the RNA-binding proteins bound to a specific endogenous RNA. In-depth understanding of the Cas13 complex, particularly as gained through structural studies, will be crucial in engineering this new arsenal.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

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