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Expression of Concern

RNase H sequence preferences influence antisense oligonucleotide efficiency

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The Authors and Editors wish to jointly publish an Expression of Concern regarding the above article.

During preparation of a follow-up manuscript, the Authors have discovered that the company which sold the commercial enzymatic preparation 'Recombinant Human RNASEH1' mislabelled the preparation. The company has confirmed that the preparation actually used a recombinant *E.coli* RNase H protein, not the human enzyme. That implies that whenever the Authors have discussed sequence preferences of the human RNase H1 enzyme, they were in fact unknowingly instead describing properties of the *E. coli* enzyme.

Below is the Authors' assessment of the consequences that the reagent mislabeling has on the major conclusions in the paper.

1. The novelty and validity of the H-SPA methodology are unaffected.
2. As a result of the mislabeling, preferences of *E. coli* RNase H were independently assessed twice, using enzyme preparations from two different suppliers and using two different reaction buffers. In the manuscript the Authors write about 'strikingly similar sequence preferences of the human and E. coli enzymes', which they interpreted as stemming from structural conservation between two enzymes, but now can only be used as an example of the method's robustness and reproducibility.
3. The explanation of the binding mode of the human RNase H1 to the RNA-DNA hybrid in the crystal structure, and correlation with mRNA knockdown may be a result of the structural similarity between human and bacterial enzymes, however those arguments are now significantly weaker.
4. The discovered competitive inhibitor of RNase H (nicked dumbbell) is a competitive inhibitor of the bacterial enzyme, not necessarily of the human enzyme.
5. The presented sequence preferences of the RNase H from HIV-1 reverse transcriptase are unaffected (figure 4).
6. The presented biological implications of the sequence preferences of HIV-1 RNase H are unaffected (figure 5).

While the Authors are preparing a new article which will address the points detailed above, the Authors and Editors wish to jointly publish an Expression of Concern to alert Readers.

The Editors commend the Authors for being forthcoming and disclosing this issue.

Keith Fox, Senior Executive Editor, *Nucleic Acids Research*

Barry Stoddard, Senior Executive Editor, *Nucleic Acids Research*

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