Correspondence

Targeting long non-coding RNAs (lncRNAs) with oligonucleotides in cancer therapy

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The Commentaries on our recent paper in *Oncotarget* (1), reporting the successful induction of apoptosis by a 23-base oligonucleotide mimicking a key section of lncRNA GAS5, have raised some important points and have further developed the broader application of lncRNA-targeting oligonucleotides in cancer therapy. This area is now attracting considerable attention, reflecting the rapidly growing awareness of the importance of lncRNAs in human cell biology and biomedicine—the numbers of citations of lncRNA papers are currently doubling every year (2), and this is recognised in all three Commentaries (3-5).

Fayda and Gezer (3) have emphasised the importance of such attempts to improve the therapy of breast cancer, in particular the therapy of triple-negative breast cancer, a particularly malignant and chemotherapy resistant form of the disease (6). They refer to one of the most important results of the original *Oncotarget* paper (1), i.e., that the 23-base oligonucleotide induced apoptosis in a triple-negative breast cancer line as well as in other breast-cancer lines. It is therefore particularly important to explore entirely novel opportunities, such as those presented by the emerging study of the lncRNAs, to produce and develop better treatments for clinically challenging cancers.

Both Fayda and Gezer (3) and Kino and Marr (4) rightly highlight the importance of future work on the lncRNA concerned, GAS5, to identify the steroid hormone receptor involved in the induction of apoptosis both by full-length GAS5 and by the 23-base oligonucleotide mimic. GAS5 does not interact with the oestrogen receptor (7), so its functional effects must be due to interaction with another, as yet unidentified, steroid hormone pathway.

Kino and Marr (4) provide further information on GAS5, i.e., that it is a host gene for small nucleolar RNAs (snoRNAs) (8,9), and go on to discuss in some detail a key remaining question—how to improve the properties of oligonucleotides, such as the GAS5 hormone response element mimic (1), for practical clinical application. One particularly encouraging factor is that the obstacles to successful clinical use for the GAS5 hormone response element mimic are broadly the same as those faced by other oligonucleotide therapies, and these are being addressed enthusiastically by many laboratories because of the immense potential of highly specific therapies targeting a range of RNAs. The three Commentaries recognise that the *Oncotarget* paper (1) helps to provide proof-of-principle for the use of oligonucleotides targeting lncRNAs, and so may be adapted for other lncRNA classes, such as those involved in the control of transcription (e.g., in epigenetic mechanisms), RNA processing and cell signaling pathways [reviewed by Morris and Mattick (10)]. Since most of the genome encodes lncRNAs (in contrast to the 2% or so that encodes protein-coding RNAs), we can deduce that the number of possible targets for improved cancer therapies

is likely to be very large and the broad exploitation of this approach may prove very productive.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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