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Doubts cast on the molecular mechanism of 'read-through' drug PTC124/Ataluren

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A drug developed to treat genetic diseases such as Duchenne muscular dystrophy and cystic fibrosis may need a radical rethink. In a new study published on 25 June in the open access journal *PLOS Biology*, researchers question the mechanistic basis of the drug called PTC124 (also known as Ataluren), casting doubt as to whether it has the molecular effects that are claimed for it. This may have implications for its effectiveness in treating genetic diseases.

An estimated 10% of all human genetic diseases are caused by nonsense mutations. These cause ribosomes to stop dead in their tracks, leaving the proteins that they are making incomplete, often with devastating effects. For example, a subset of cases of cystic fibrosis are caused by nonsense mutations in the gene encoding CFTR, a transmembrane chloride ion channel. The vision behind PTC124, one of a class of so-called "read-through" drugs, was to trick the ribosome into ignoring these premature stop signs, so that enough full-length protein could be made to substantially improve the lot of patients. PTC124 was initially shown to be effective in promoting read-through of mutations that cause Duchenne muscular dystrophy, a severe, lethal and relatively common genetic disease. Subsequently, however, despite some positive results, reports of PTC124's efficacy for this and other genetic diseases have been mixed, and people in the field have started to question the efficacy of the drug.

In the new study, Stuart McElroy, Irwin McLean and colleagues at the University of Dundee question the validity of the elegant screening

experiment initially used to identify PTC124. This was based on a system whereby an effective read-through drug would cause the ribosomes to make a "reporter" enzyme named luciferase; this enzyme was originally isolated from fireflies, and can be detected by its ability to produce light. McElroy and colleagues confirmed previous studies that suggested PTC124 instead deceives the drug screening system via a direct effect on the luciferase enzyme, rather than by causing read-through. They then showed that this doesn't occur when they used alternative reporter enzymes. But does PTC124 nevertheless cause translational read-through? The answer, apparently, is no; the authors went on to systematically test the effects of PTC124 on the read-through of all possible nonsense mutation contexts and on a range of scenarios. In each case, PTC124 failed to show any effect. The originally reported effects are therefore likely to have occurred by some mechanism other than read-through.

It should be noted that McElroy and colleagues only tested cells (not intact animals), that they only look at read-through activity, and that there are several publications suggesting clinical efficacy of PTC124 (particularly for cystic fibrosis) that are not challenged by this study. It is well known that some drugs may act by means other than originally intended but nevertheless remain effective. However, the study does raise questions about the drug's mechanism and efficacy for genetic diseases, indicating that in instances where PTC124 does have beneficial effects, this may be down to serendipity rather than the purported mechanism of translational read-through.

More information: McElroy SP, Nomura T, Torrie LS, Warbrick E, Gartner U, et al. (2013) A Lack of Premature Termination Codon Read-Through Efficacy of PTC124 (Ataluren) in a Diverse Array of Reporter Assays. PLoS Biol 11(6): e1001593. doi:10.1371/journal.pbio.1001593