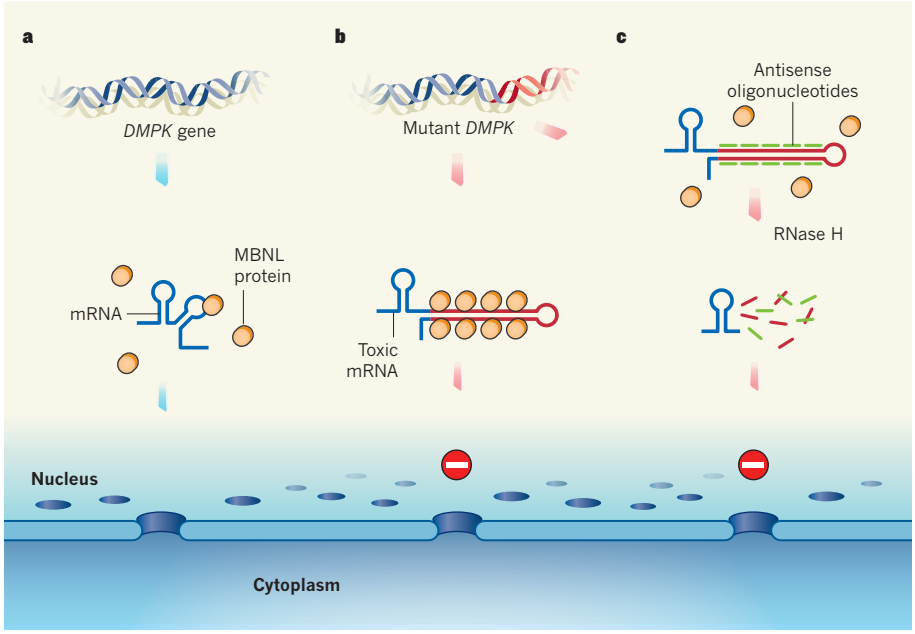

Figure 1 | How to silence a toxic RNA. **a**, Most messenger RNAs, such as that encoded by the *DMPK* gene, are processed by splicing proteins and then rapidly exported from the nucleus into the cytoplasm, where they are translated into proteins. MBNL splicing proteins interact with many mRNAs, including the *DMPK* mRNA. **b**, Expansion of a repeat region in *DMPK* mRNA causes myotonic dystrophy type 1 by sequestering MBNL proteins and retaining them in the nucleus, thereby affecting the splicing and expression of many cellular RNAs. **c**, Wheeler and colleagues[5] describe the successful use of antisense oligonucleotides (short RNA-like molecules) to ameliorate the disease's symptoms in a mouse model. The oligonucleotides bind to the mutant RNA and selectively induce its destruction in the nucleus by the enzyme RNase H.

and correction of RNA splicing defects and the resultant myotonia. Astonishingly, the most effective oligonucleotides continued to confer some benefit up to a year after treatment had been discontinued.

Animal tests of RNA-directed therapies for muscle diseases such as DM1 have had limited success so far[7–9]. So, why this apparent breakthrough? It comes down to the therapy's probable site of action: the nucleus. Most mRNAs are synthesized and spliced in the nucleus, then rapidly exported to the cytoplasm. But gapmer oligonucleotides induce degradation of RNA by RNase H, which is enriched in the nucleus and almost absent from the cytoplasm. Wheeler and colleagues, and a second research group working independently[9], reasoned that the nuclear retention of expanded-repeat RNAs could make them good targets for RNase H. Consistent with this idea, the authors describe how oligonucleotides designed to target RNAs that are rapidly exported to the cytoplasm were ineffective at decreasing their expression in muscle. By contrast, oligonucleotides targeting a nuclear RNA (the long non-coding RNA *Malat1*) demonstrated similar efficacy to that seen when targeting the expanded-repeat RNA.

What are the implications of Wheeler and colleagues' results? They inspire optimism that previous challenges faced by researchers looking at antisense oligonucleotide therapies for DM1 and other neuromuscular diseases are surmountable — although significant hurdles remain regarding safety and delivery to affected tissues other than skeletal muscle, such as the heart and brain. The authors' findings also suggest that gapmer-based strategies might be suitable for the treatment of other disorders caused by expansions of repeated DNA sequences (such as amyotrophic lateral sclerosis and frontotemporal dementia[10,11]), provided that the mutant RNA tends to remain in the cell's nucleus longer than the normal RNA. Furthermore, appropriately designed gapmer oligonucleotides may aid researchers in defining the functions of specific nuclear non-coding RNAs, some of which have key roles in regulating gene expression.

However, as promising as these findings are for the prospect of DM1 therapeutics, they also serve as a cautionary tale for the applications of antisense oligonucleotides. First, given our limited understanding of the roles of nuclear non-coding RNAs and the likelihood that their sensitivity to this technology is enhanced, care must be taken in oligonucleotide design to avoid potentially deleterious off-target effects. Second, developing similarly potent therapies for target mRNAs that are rapidly exported from the nucleus may require the use of oligonucleotides that do not act through RNase H. Third, therapeutic success in a mouse model is still a long way from effective application in humans. However, the path to success now seems clearly visible. ■

50 Years Ago

The importance of lunar natural resources for the future of space exploration can scarcely be exaggerated. Lunar resources will not only play an important part in the establishment of a lunar base by providing life support materials and vehicle fuels but will also be an important, and perhaps a limiting, factor in the logistics of interplanetary space exploration. Certainly, only the most cursory exploration of the solar system could be conducted using either existing or planned propulsion systems so long as the rocket vehicles must lift all their fuel from the surface of the Earth. A lunar fuel source, on the other hand, would provide an extremely convenient low-gravity refuelling station in space.

From *Nature* 4 August 1962

100 Years Ago

A note bearing on the much-debated question of the age of the earth is given in the Proceedings of the Tokyo Mathematico-physical Society by S. Suzuki. The calculation refers to the time taken for the present crust of the earth to solidify. A result is obtained on the supposition that the heat of fusion liberated by the solidification of the crust supplies the heat lost by radiation, and it is further assumed that the effect of the curvature of the earth's surface may be neglected. According to these hypotheses the calculated time varies between 30 and 300 million years, according to the kind of rock (gneiss, basalt, or granite) assumed in the calculations. The difficulty is, of course, our imperfect knowledge of the experimental data on which the conclusions are based.

[Editor's note: Latest estimates give Earth's age as 4.5 billion years.]

From *Nature* 1 August 1912