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What history tells us

XXXX.

The success story of the expression “genome editing”

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1. Introduction

The expression “genome editing” is now routinely and unproblematically used to designate the fundamental and applied uses of the newly custom-designed “scissors” of DNA, led by CRISPR Cas9 - see for instance the last 2015 issue of *Science* (McNutt 2015; Travis 2005).

It is fascinating to observe “in real time” this rapid change in scientific vocabulary. I was too young to see with my own eyes the introduction of the informational terms in molecular biology, but I have the premonition that we are living a similar event, with identically dramatic consequences.

Such phenomena are particularly appealing to the historian: the word is already there, with different meanings. Its rapid adoption for something new is a collective and tacit decision of the scientific community, but also a global cultural phenomenon since the word and its meanings do not belong to science alone.

As a French-speaking observer, there was an additional reason

to describe this event. In the French language, “éditer” means “to publish”. But in recent years, with the increasingly important place of computers in publishing houses, and the increasing import of English words, the expression “éditer un texte” *i.e.* “to edit a text” has progressively been introduced to describe the complex work done on a manuscript to improve it. Since for a text to be published, it has to be “edited”, the transition was smooth. A parallel but different shift in the meaning of “editing” occurred in the French language and in biology. In both cases, computers played an important role. I will successively consider the early and diverse uses of “editing” in molecular biology. Then I will examine the recent use of “genome editing”, the rational justification of this new use in 2010, as well as its previous unjustified and progressive uses since the beginning of the 2000s, and the favourable context in which this introduction occurred. I will draw some final conclusions from this historical episode. The background of this “linguistic turn” is the discovery of the CRISPR Cas9 system and its possible applications, which are described in two previous publications (Morange 2015a and 2015b).

2. The early uses of “editing”

All molecular biologists are familiar with the phenomenon of RNA editing discovered in the mid-1980s (see later). When the word “editing” is entered in PubMed, a large part of the articles that are selected is devoted to RNA editing.

But the first uses of the word “editing” in molecular biology were different. They referred to the transfer of information between DNA and proteins, and to the capacity of the enzymes and proteins that are involved to correct the errors that might occur in this process. Alan Fersht devoted many studies in the 1970s to the capacity of aminoacyl tRNA

synthetases to control the nature of the amino acid that has been loaded on the transfer RNAs, and to remove it when it is not the right one (Fersht 1980).

The editing or proofreading capacity of DNA polymerase, and in particular of the famous Klenow fragment of DNA polymerase I extensively used in genetic engineering, was scrutinized. The reliability of the information stored in DNA was not the consequence of the chemical stability of this macromolecule, but of these editing processes as well as of the repair mechanisms (Loeb and Kunkel 1982).

Editing was first used for RNA to describe the complex processes that led from DNA transcription to the formation of a translatable RNA: maturation of the RNA at the 3' end after termination of transcription, with addition of a polyA tail. The splicing process by which long RNA transcripts are cut and the fragments pasted to generate messenger RNAs was sometimes also included in the editing process (Lewin 1983).

A new meaning of RNA editing resulted from the study of the transcription of mitochondrial DNA in trypanosomes (Benne *et al.* 1986): the sequences of RNAs were corrected, sometimes extensively, by the insertion/deletion of nucleotides and/or the modification of some others, such as the conversion of adenosine to inosine. RNA editing was shown not to be limited to kinetoplastid protozoa, and was also observed in plant mitochondria (Gualberto *et al.* 1989; Covello and Gray 1989) and animals. In the latter, editing of the RNAs encoding the apolipoprotein B and neuroreceptors of the central nervous system has been extensively studied (see, for instance, Reenan 2001). In 1990, it was demonstrated that RNA editing in kinetoplastid protozoa required guide RNAs (Blum *et al.* 1990), exactly as 22 years later the CRISPR Cas9 enzyme, on the eve of becoming the most popular genome editing tool, was shown to depend on guide

RNA for its action.

The word “editing” was also used in the 1990s for the receptors of the immune system: their precise structure results from a complex process of reassortment of genetic material and selection among the different cellular clones produced (Gay *et al.* 1993; Tiegs *et al.* 1993).

In all the cases that we have so far described, editing was a natural process, probably the result of the optimizing action of natural selection, leading to proteins with the right structure (although the complexity and diversity of the RNA editing process early suggested that it might have other functions). Another use of the word “editing” entered molecular biology through the increasing role of computers in this discipline. The development of libraries required editing of the information put in them (Linhart *et al.* 1980). Genome sequencing programmes dramatically increased the amount of information that was stored in these libraries. The word “editing” was used for the complex process of annotation of genomes (Lewis *et al.* 2002), in the same way as chemists edit their NMR spectra. But the increased use of this word in biology was mainly the result of the complex process of sequence assembly generated by shotgun experiments, and the more and more time-consuming elimination of errors that might have occurred during the sequencing step itself (Arner *et al.* 2006). Editing a genome is an expression that became familiar to bioinformaticians. It was no longer nature (organisms) that edited, but researchers. However, computer scientists when editing were aiming at describing DNA sequences as they exist in nature.

3. Editing the genome

From correcting the sequences produced by machines and programmes to correcting the sequences that have been altered by mutations, there was a short distance that was progressively stepped over in the 2000s.

In 2010, Fyodor Urnov and his colleagues made explicit the reasons for adopting the expression “genome editing” to designate the use of the newly designed DNA scissors: the fact that they cut at precise positions in the genome with a limited number of off-targets, that their action does not lead to the insertion in the genome of additional sequences, and that they permit the efficient replacement of a mutated copy of a gene by a normal version of it were all good reasons to speak of “genome editing” (Urnov *et al.* 2010).

2010 was three years before “the CRISPR craze” (Pennisi 2013) and two years before the publication by Jennifer Doudna and Emmanuelle Charpentier that ignited the field (Jinek *et al.* 2012). This demonstrates that the introduction of the expression “genome editing” and its slowly increasing use preceded the discovery of the potential of the CRISPR Cas9 system. Its roots were in the progressive development of tools to modify DNA sequences, by using first modified single-stranded oligonucleotides and then specific nucleases (meganucleases, recombinases, zinc finger proteins coupled to a nuclease). Evidence progressively accumulated that these nucleases were not only tools well adapted to gene inactivation or gene insertion, but also dramatically increased the efficiency of homologous recombination and therefore permitted highly efficient gene replacement – the first evidence being provided by Puchta *et al.* 1993 and Rouet *et al.* 1994. 2003 was a crucial year: zinc-finger nucleases proved efficient in inactivating genes and in substituting normal copies for mutated ones, which opened the perspective of

using them for therapeutic applications (Bibikova *et al.* 2003; Porteus and Baltimore 2003).

There were plenty of expressions—“gene targeting”, “genome engineering”, “gene correcting”—likely to be used to designate these new practices. “Genome editing” with this new meaning was first used at the beginning of the 2000s (Balbas and Gosset 2001; Stark and Akoplan 2003, Gruenert *et al.* 2003), and the expression progressively became more widespread in subsequent years. The main researchers involved in the development of these new tools, such as Dana Carroll and Srinivasan Chandrasegaran (Durai *et al.* 2005; Carroll 2008), were far from being the strongest supporters of the new vocabulary.

Interestingly, in the same years, there were new observations demonstrating the extent of RNA editing that paradoxically brought into question its physiological significance (Nishikura 2004). RNA editing was no longer a sufficiently attractive field of research to prevent the word “editing” from being borrowed for the description of other phenomena.

4. Conclusions

The expression “genome editing” is the new use of the word “editing” whose mundane meaning allowed it to be recurrently employed by biologists. Nobody controlled this new introduction, and those who were the most eager to seize the potential of this word were not always the most active in producing data supporting its new use.

Despite lacking a clearly identified father, this new use is highly significant. It represents a shift from a natural to an artificial meaning of the word. Before, nature edited; now, biologists edit, and by doing so they correct and improve nature. The word is well chosen to make the new practice acceptable. It emphasizes the fact that the results of biologists’

practice will be precise, and “clean”. But this expression is also the extension of the hope invested in genome sequencing programmes: whereas the latter seek to read the book of life, the new projects aim to edit it.

The main risk for the expression “genome editing” stems from its success. It is already used for “gene drive” and for crop and animal “enhancement” projects, where the work of biologists is not directly aimed at correcting the book of life. The price to pay for this undue extension may be a weakening of its power of attraction.

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