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about what, where, for which purposes, who, and how many animals are to be used in the proposed research. Raised awareness is a key first step to allow public stakeholders to debate and judge the uncertainties and transformative potential of genome-editing technologies.

The French Connection

In 2015 a group of researchers and ethicists from France and neighboring countries, initiated by the National Institute for Health and Medical Research (INSERM) Ethics Committee, began organizing a series of meetings in Europe, India, Africa, and South America, addressing the diverse ethical issues associated with the responsible use of genome editing as applied to humans, animals, plants, and the environment. The initial position of this group, projected from Europe, was first reported in early 2017.3 The proposal was expanded upon in a longer paper published last summer that proposed the creation of a European Steering Committee to assess the potential benefits and risks of genome editing, design risk matrices and scenarios for responsible uses of this technology, and contribute to an open debate on societal aspects prior to a translation into national and international legislation.4

In November 2017, INSERM held an important meeting in Paris to examine many existing reports, position papers, and manifests on the ethical and societal aspects of genome editing and the responsible uses of these technologies (reviewed by de Lecuona et al.).5 We wanted to go beyond the publication of a simple report: we wished to become useful, operative, proactively engaging the various stakeholders mentioned above in this debate.

From that meeting, it also became clear that the scope of this initiative had to be truly international, going beyond the usual perspectives from Europe, North America, China, Japan, and Australia and involving the oft-forgotten south by including members from Southeast Asia, Africa, and Central/South America. Those discussions crystallized in the March 23, 2018, conference at Île-de-France regional Parliament in Paris, featuring approximately 160 participants from 35 countries. Here we decided to launch the ARRIDGE initiative (Fig. 1).

The aim of this new nonprofit initiative is to promote a global governance of genome editing through a comprehensive setting for all stakeholders—academics, researchers, clinicians, public institutions, private companies, patient organizations, and other nongovernmental organizations, regulators, citizens, media, governmental agencies, and decision makers from all continents. We hope to address multiple issues raised by genome-editing technologies used in research and applications within a safe and ethical framework for individuals and society.

More specifically, the ARRIDGE association aims to provide a vehicle for meetings and outreach with the following four major objectives:

1. fostering an inclusive debate with a risk-management approach, considering human, environmental, animal, and economic issues;
2. getting involved in the governance of genome-editing technology with governmental and intergovernmental stakeholders;
3. creating an ethical toolbox and informal guidance for genome-editing technology users, regulators, governance, and the civil society at large, including those living in low- and middle-income countries; and
4. developing a robust and specific reflection on the role of the lay public in this debate and the necessity for improved public engagement.

Coincidentally, the same week of our March meeting in Paris, a similar proposal was published in Nature, suggesting the creation of a global observatory and requesting a cosmopolitan conversation on the uses, applications, and consequences of genome editing technologies.6 These proposals were independent of each other. However, thanks to media outreach,7 we look forward to working collaboratively in pursuit of our common aims and interests.

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*For more information, contact the ARRIDGE initiative (join@arrige.org) and/or visit the ARRIDGE web site, which hosts various documents, talks, and videos (http://arrige.org).
It’s CRISPR Clear: Off-Target Study Misses the Mark

Shondra M. Pruett-Miller

A Controversial 2017 Nature Methods Report Raising Concerns About Off-Target Genome Editing in Mice Has Been Retracted

When you were little, did you ever hear a bump in the night and assume the worst? The noise could be a scary monster, the neighbor’s cat, or just your kid sister. It’s only natural to assume the worst, but assumptions are not conclusive—especially without proper controls.

In May 2017, a group led by Stanford University physician-scientist Vinit B. Mahajan published a brief report in *Nature Methods* that claimed that CRISPR*-Cas9* edited mice had a multitude of unexpected mutations.1 The study gained widespread attention and hurt the stock prices of several CRISPR-based biotech companies. After sequencing only two edited mice, the authors tallied the widespread genomic differences between a strain control animal (Fig. 1) maintained in a separate colony and the two edited animals and attributed these differences to off-target effects of the CRISPR treatment. (The CRISPR treatment involved zygote injections of one single guide RNA [sgRNA] plasmid, Cas9 protein, and an oligo donor. Of note, the use of a sgRNA expression plasmid along with Cas9 protein was unconventional because of temporal expression differences. Furthermore, important details such as which sgRNA expression plasmid and Cas9 protein were injected were not included in the original publication.)

This study quickly drew criticism: within a couple of weeks, the journal issued an editorial note explaining that “the conclusions of this paper are subject to criticisms that are being considered by editors.”1 A month later, *Nature Methods* added an editorial “expression of concern” and warned that “since the background genetic variation between the control mouse and the CRISPR-treated animals is not known, an alternative proposed interpretation is that the observed changes are due to normal genetic variation.”1

On March 30, 2018, the journal finally issued a formal retraction, stating that “without proper controls or more analysis of genetic background, it is not certain that the variants reported are due to CRISPR treatment.”1 The retraction (approved by just two the original six authors) was accompanied by the publication of five letters to the editor, including correspondence from several CRISPR biotech companies, critiquing the original paper.2–6 A *Nature Methods* editorial acknowledged that the originally selected referees lacked expertise in the genetic variation of inbred mouse strains.7

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*Clustered Regularly Interspaced Short Palindromic Repeats.*

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