

Controversy and debate: the nature of science

Controversy is an
integral part of
scientific discovery

Biological research is rarely definitive, and experimental evidence for a particular model can often be considered more or less convincing at best. It is the very nature of science that most models are merely “works in progress” which only remain valid until they are supplanted by a refined model or are proven wrong and discarded.

It is therefore hardly surprising that peer-reviewed and published results are sometimes irreproducible in a different experimental context or when subjected to more sensitive analysis; results *in vitro* may not reflect the complexity of the situation *in vivo*. In addition, experiments may be poorly performed or simply vary for undefinable reasons. As a publisher of primary research, we believe that we are obliged to take seriously any refutations of results that we publish, and to publish those that are convincing. Our procedure is first to give the authors of the refuted publication the opportunity to respond; both the refutation and the response are then rigorously peer reviewed, ideally by the referees of the original paper. This procedure allows scope for the refuted authors to have their say, it quickly resolves differences of a clearly technical nature, and it circumvents the possibility that the refuted author might block publication of the refutation. If the reviewers believe that the manuscript raises legitimate, convincing questions on the validity of a key claim, we will publish the refutation, on the grounds that if the original claim was judged to be of broad interest, the fact that it is not reliable is presumably also of equal interest.

This issue contains an example of a refutation as well as correspondence relating to a previous refutation. In May 1999, we published a paper from Sherr and colleagues that showed that the tumour suppressor protein, p14^{ARF}, sequesters Mdm2 in the nucleolus, thereby preventing it from antagonizing the function of the tumour suppressor protein, p53 (*Nature Cell Biol.* 1, 20-26 (1999)). Another paper published in our pages from Vousden and colleagues added further support for this model (*Nature Cell Biol.* 2, 179-181 (2000)). On page 445 of this issue, Peters and colleagues provide evidence that in at least some situations in which p53 is stabilized, Mdm2 is not localized to the nucleolus, and ARF is able to antagonize its function without itself localizing to the nucleolus. The exact reasons for the experimental discrepancies between these papers remain unclear; nevertheless, the extent to which nucleolar sequestration of Mdm2 by p14^{ARF} contributes to its negative effect on the Mdm2-p53 pathway is an issue ripe for further study and debate.

In another example, in December 1999, Imaizumi and colleagues showed that in the presence of certain mutations in presenilin that are linked to familial Alzheimer's disease (FAD), the unfolded protein response (UPR) is downregulated (*Nature Cell Biol.* 1, 479-485 (1999)). This suggested that an impaired UPR, which normally deals with situations of cellular stress, might contribute to the development of this disease. Later, however, Thinakaran and colleagues did not observe any effects of the UPR in the presence of FAD-linked PS1 mutations (*Nature Cell Biol.* 2, 863-870 (2000)). The final chapter in this story is a Letter to the Editor from Imaizumi and colleagues on page E104 of this issue, stressing that the discrepancies between the two papers are quantitative and are apparently sensitive to both experimental conditions and the selection of time points. Future investigations will determine under which circumstances presenilin mutations might affect the UPR and, perhaps most importantly, whether the UPR has a role in the pathogenesis of FAD.

These examples illustrate that controversy is an integral part of scientific discovery, and often helps to spur progress. Our responsibility as publishers of primary research is to ensure that substantial criticisms are allowed similar opportunities for publication if, on careful consideration, they appear to be valid. □