Unintended Consequences and Artifacts

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IN THIS ISSUE, there are two articles on which I wish to comment: the first, as a caution to other laboratories and researchers to exert extra care in their observations, and the second, to emphasize that some powerful techniques may be imperfect when applied, yielding results that may be artifacts.

Many investigators survey the association of polymorphisms for virtually every possible gene and try to associate alleles or single-nucleotide polymorphisms (SNPs) with some syndrome. In most cases, without solid data showing a consequence of the polymorphism (amber mutation, loss of splice site, altered amino acid, altered half-life of mRNA or protein, aberrant protein activity, loss of post-translational modification, for instance) association as a molecular mechanism of disease, the Editors of this journal do not send such a manuscript out for peer review; we refer the authors to clinical journals in their field. In the case of Huang *et al.* on page 654, the meta-analysis finding was that the polymorphism in a cytokine gene yielded absolutely no biologic consequence when several conflicting studies were assessed. This should alert other laboratories that they must exert care in extrapolating from an observation of an SNP difference in a group, and these laboratories must demonstrate clear cause and effect between genetic sequence variants, biological function, and disease pathogenesis.

The second concern is the under-appreciated potential for artifacts in observations when laboratories construct reporters because the modification of protein sequence can dramatically alter the structure, function, and intracellular location, as Costantini and Snapp, in the DNACB Bit starting on page 622 of this issue, elegantly demonstrate. Tagging proteins with reporters such as the green fluorescent protein (GFP) is a very common practice, and can be a powerful way of following gene expression, viral infection, or many other applications. However, as Costantini and Snapp illustrate, this is an imperfect technique, and data must be interpreted with that caveat in mind.

That said, I would like to make it absolutely clear that the articles noted above are high quality and passed our rigorous peer review process. I mention these articles as clear examples to the scientific community to be aware of the technique and to pay close attention to the details hidden within their research, results, and data.

On a related and more serious topic, the U.S. Federal budget crisis, secondary to the economic downturn, which led the Congress to create the "Sequester," has led to 700 fewer grant applications funded and thousands of existing grants receiving far less than they need to accomplish the approved/funded work. This contraction impacts not only individuals associated with those laboratories, but potentially a larger cohort of trainees who will no longer be able to do the research and therefore not complete their training. Other young scientists will be discouraged and potentially leave biomedicine. If research in other countries had brighter prospects, these scientists would try to relocate, but unfortunately, this problem is not restricted to the United States and the NIH is by far the largest agency that supports research. So, an unintended consequence of the failure of the Congress to raise taxes to pay for essential programs that they authorized may be a long-term loss of a significant portion of a generation of young scientists. We, my Associate Editors and I, hope that the Congress realizes the impact of this flawed policy very soon and corrects it.